30 July 2015
EMA/CHMP/535898/2015 Rev 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fexeric

Ferric citrate coordination complex

Procedure No. EMEA/H/C/003776/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

A/G	albumin/globulin ratio
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BET	Brunauer–Emmett–Teller
CHMP	Committee for Medicinal Products for Human use
CPMP	Committee for Proprietary Medicinal Products
CKD	chronic kidney disease
CKD 5D	CKD dialysis (stage)
CKD ND	CKD non-dialysis (stages)
C_{max}	peak concentration
CNS	central nervous system
Creat	Creatinine
DG	day of gestation
DMT-1	divalent metal ion transporter 1
DNA	deoxyribonucleic acid
DRF	dose range finding
EAP	Efficacy assessment period, Efficacy analysis population
EC	European Commission
EDTA	Ethylenediaminetetraacetic acid
ESA	erythropoiesis stimulating agent
ESKD	End stage renal disease
EU	European Union
GC	Gas chromatography
GGT	gamma-glutamyl transpeptidase
GI	Gastrointestinal

GIT	gastrointestinal tract
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	good laboratory practice
GMP	Good manufacturing practice
HD	Haemodialysis
HDPE	high density polyethylene
HED	human equivalent dose
HGB	Haemoglobin
HP	hyperphosphatemia
HPLC	High performance liquid chromatography
HPT	hyperphosphatemia
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
i.m.	intramuscular
i.p.	intraperitoneal
IPC	In-process control
IR	Infrared
IUPAC	international union of pure and applied chemistry
ITT	intent-to-treat
IV	intravenous
KF	Karl Fischer titration
KRX (KRX-0502)	Ferric citrate complex (a special construct of ferric citrate (formulation proposed for marketing)), Fexeric
Kt/V	Dialysis adequacy measure
LoD	Loss on drying
MAH	Marketing authorisation holder
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration

MCV	mean corpuscular volume
MPV	mean platelet volume
MRHD	maximum recommended human dose
MTD	maximum tolerated dose
NMR	Nuclear magnetic resonance
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	organisation for economic co-operation and development
P	phosphorus
Pi	inorganic phosphorus
PCE	polychromatic erythrocyte
PCS	Potentially clinically significant
PD	parenteral dialysis
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PT	prothrombin time
PTH	parathyroid hormone
QTc	corrected qt interval
RBC	red blood cell count
RDW	red cell distribution width
RES	reticuloendothelial system
RH	relative humidity
s.c.	Subcutaneous
SmPC	Summary of product characteristics
SP (SAP)	Safety assessment period (safety analysis population)
Tbili	total bilirubin
TG	Triglycerides
TIBC	total iron binding capacity
t_{max}	time to peak concentration
TP	total protein
TEAE	treatment-emergent adverse event

TSAT	transferrin saturation
UIBC	unsaturated iron binding capacity
USAN	united states adopted name
UV	Ultraviolet
WBC	leucocyte count
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Keryx Biopharma UK Ltd. submitted on 7 March 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Fexeric, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 May 2013.

The applicant applied for the following indication: Fexeric is indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC -complete and independent application. The applicant indicated that Ferric citrate coordination complex was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0183/2013 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0183/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance Ferric Citrate Coordination Complex contained in the above medicinal product to be considered as a new active substance in comparison to the known Ferric Ammonium Citrate previously authorised in the Union (e.g, Minadex Tonic) and claimed that Ferric Citrate Coordination Complex differs significantly in properties with regard to safety and efficacy from the already authorised substance.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 14 April 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier. The Applicant partially followed the Scientific Advice given.

Licensing status

In January 2014, ferric citrate coordination complex (invented name: Riona; MAH: Japan Tobacco) was approved in Japan for the treatment of hyperphosphataemia in adult patients with CKD. The Applicant explained that parts of this application served as the basis for the approval of ferric citrate coordination complex in Japan, and also formed the basis of a New Drug Application submission to the US FDA on 7/08/2013 (NDA-205874). NDA-205874 was accepted for review by FDA on 7/10/2013 and approved on 5/9/2014.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Romaldas Mačiulaitis Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 7 March 2014.
- The procedure started on 26 March 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2014.
- During the meeting on 10 July 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 24 July 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 January 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 March 2015.
- During the meeting on 12 March 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 June 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 July 2015.
- During the meeting on 9 July 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 23 July 2015, the CHMP, in the light of the overall data submitted and the scientific

discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Fexeric.

- The New Active Substance Report was adopted via written procedure on 30 July 2015.
- A revised CHMP opinion and Assessment Report were adopted by the CHMP on 30 July 2015 in order to reflect the NAS status and conduct of PASS.

2. Scientific discussion

2.1. Introduction

Hyperphosphataemia (HP) is an electrolyte disturbance characterised by increased serum phosphorus, related to imbalance in the dietary phosphate intake and excretion in the urine. Increased serum phosphorus levels results in: Stimulation of parathyroid hormone (PTH) secretion and parathyroid gland hyperplasia, with the development of secondary hyperparathyroidism and Changed overall calcium/phosphorus balance in the body; increased calcium × phosphorus ion product (Ca ×P) and extra-skeletal phosphorous-calcium precipitation. Serum phosphorus levels generally increase when glomerular filtration rate (GFR) falls below 40 mL/min/1.73 m^2 (CKD stage 3). When GFR falls to <20 mL/min/1.73 m^2 (CKD Stages 4 and 5), around 40% of patients have elevated phosphorus levels. Almost all patients with CKD Stage 5 will have hyperphosphataemia.

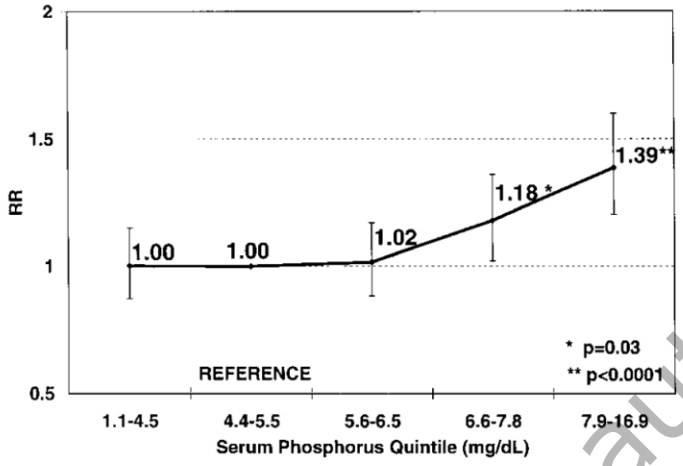
The term *phosphorus* is used interchangeably with *phosphate*. Although the majority of phosphorus in the body is in the organic form – complexed with carbohydrates, lipids and proteins, most extracellular phosphorus is in the inorganic form (P_i). Serum phosphorus/phosphate (P_i) measurements reflect the sum of two physiologically occurring inorganic ions: hydrogenphosphate (HPO_4^{2-}) and dihydrogenphosphate ($H_2PO_4^-$).

The reduction in GFR reduces phosphorus excretion and results in: (i) Hyperphosphataemia; (ii) Decreased 1,25-dihydroxyvitamin D (1,25(OH)2D) levels; (iii) Elevated PTH (which would normally stimulate phosphorus excretion and calcium reabsorption) levels; and (iv) Elevated fibroblast growth factor-23 (which promotes phosphorus excretion and reduces 1,25(OH)2D synthesis) levels.

With loss of kidney function, progressive disruption of mineral homoeostasis occurs, affecting calcium, phosphorus, vitamin D, and PTH. A vicious cycle develops, in which phosphorus-stimulated secretion of PTH stimulates the release of calcium and phosphorus from bone, and inhibits bone formation and mineralisation. The mineral disturbances impair bone modelling, remodelling and growth. In addition, high serum calcium and phosphorus levels can lead to extraskeletal calcification. CKD-mineral and bone disorder is used to describe this syndrome of abnormal mineral metabolism, abnormal bone and extra-skeletal calcification that develops as a result of CKD.

Relationship between serum phosphorus levels and mortality in patients with CKD is provided in Fig. 1. Haemodialysis patients with serum phosphorus >6.5 mg/dL (2.10 mmol/L) had an increased risk of death (relative risk 1.27) compared with patients with serum phosphorus from 2.4 to 6.5 mg/dL (0.77 to 2.10 mmol/L).

Figure 1. Relative Mortality Risk by Serum Phosphate Quintiles



Data Source: Block GA et al, 1998 [8]

The aim of treatment of hyperphosphataemia (HP) differs considering various CKD populations and various panels of experts. In dialysis patients the aim is to reduce phosphorus (P) levels towards a definitive value of 1.78 mmol/L (5.5 mg/dL), according to the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines, or towards a normal range with flexible individualised therapy based on patient conditions, according to the KDIGO guidelines. The non-dialysis CKD population needs stringer (KDOQI) or the same (KDIGO) targets (see Table **1**)

Table 1: Recommended target ranges for serum P_i levels

Guideline	Recommended serum P_i range	
	CKD ND	**CKD 5D**
US KDOQI	0.87 to 1.49 mmol/L (2.7 to 4.6 mg/dL)	1.13 to 1.78 mmol/L (3.5 to 5.5 mg/dL)
KDIGO	Maintain serum P_i in normal range (0.81 to 1.45 mmol/L; 2.5 to 4.5 mg/dL)	Lower serum P_i towards normal range (0.81 to 1.45 mmol/L; 2.5 to 4.5 mg/dL)
UK Renal Association	0.9 to 1.5 mmol/L (2.8 – 4.6 mg/dL	1.1 to 1.7 mmol/L (3.4 to 5.3 mg/dL)

These clinical practice guidelines recommend both dietary management and the use of phosphate binders (in addition to dialysis in CKD 5D) to control serum P_i levels. In both HD and PD patients, phosphate removal by conventional dialysis modalities is inadequate to maintain neutral phosphate balance even in phosphate-restricted diets.

All these aspects need to be considered for development of the new P binding drug.

About the product

KRX-0502 (ferric citrate coordination complex, also referred to as Fexeric, ferric citrate or JTT-751) is an oral iron-based phosphate binder. In the context of treatments for hyperphosphataemia, it can be considered a calcium-free phosphate binder. KRX-0502 reduces intestinal absorption of dietary phosphate by binding to and then precipitating phosphate in the gastrointestinal (GI) tract. Ferric [Fe3+] iron reacts with ingested phosphate to form an insoluble ferric phosphate complex, which is not absorbed or metabolised during GI transit and is excreted in the stool.

KRX-0502 drug substance is produced by a patented granulation process yielding a very high specific surface area, leading to a significantly higher phosphate binding capacity as compared to ferric citrate from a commercial source.

The proposed starting dose of KRX-0502 is 3−6 g per day (in divided doses with or immediately after meals), which may be titrated up to a maximum dose of 12 g/day, with the goal of maintaining serum phosphorus within the desired range. The maximum recommended human dose (MRHD) corresponds to about 2.52 g ferric iron/day (28 to 42 mg Fe3+/kg/day) and 7.2 g citrate/day (80 to 120 mg citrate/kg/day), for patients of 90 or 60 kg, respectively.

Type of application and other comments on the submitted dossier

- Legal basis

Marketing authorisation application for a new medicinal product Fexeric (Ferric Citrate Coordination Complex) has been made pursuant to Article 8(3) of Directive 2001/83/EC, as amended, in accordance with Council Regulation (EC) No.726/2004.

- Significance of paediatric studies

A Paediatric Investigation Plan (PIP; Procedure No. EMA-001213-PIP02-12) submitted under Article 7 of Regulation (EC) 1901/2006 for KRX-0502 (ferric citrate) was approved on 31 July 2013 (Decision No. P/0183/2013), whereby:

- a waiver was granted for the paediatric population from birth to less than 6 months of age;
- a deferral was granted for the: (1) initiation of clinical studies (to be initiated only after the completion of a 56-day oral toxicity study in juvenile rats and interpretation of results); and (2) completion of all studies; the PIP is to be completed by September 2019.

The Applicant submitted a Request for Modification of the approved PIP with the indication of “Treatment of hyperphosphataemia and the increase and maintenance of iron stores in patients with chronic kidney disease. Treatment with ferric citrate coordination complex also leads to a reduction in concomitant IV-iron and ESA use in CKD patients receiving dialysis” on April 28th, 2014 The review of this request for modification was intended to be started on May 21st and the day 60 of the procedure would be planned for July 16-18 2014.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 1 g of ferric citrate coordination complex as active substance.

Other ingredients are:

Tablet core: pregelatinised starch; calcium stearate.

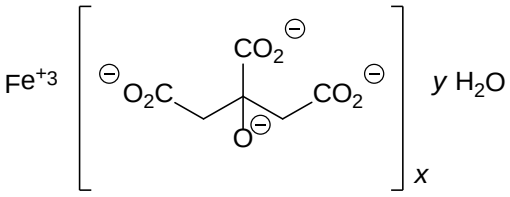
Film-coating: hypromellose; titanium dioxide; triacetin; Sunset Yellow FCF (E110); Allura Red AC (E129); Indigo Carmine.

The product is available in HDPE bottles with child-resistant closure and desiccant as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of ferric citrate coordination complex is iron (III)-(2-hydroxy-1,2,3-propanetricarboxylic acid)$_x$(H_2O)$_y$ and has the following structure and properties:



Relative molecular mass: 244.94 gmol^{-1}

The structure of ferric citrate was elucidated by high resolution mass spectrometry (positive and negative ionisation), UV spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and Mossbauer spectroscopy. However, CHMP has requested additional characterisation data on the active substance be provided on a further five commercial batches in order to fully understand the nature of the complex and the ability of the manufacturing process to reproducibly afford the same structure.

The ferric citrate complex is a light brown to beige, slightly hygroscopic amorphous solid, highly soluble in water and insoluble in organic solvents.

Different crystalline polymorphs of ferric citrate are known in the literature but all contain different counter ions. Attempts to generate crystalline polymorphs from this complex resulted only in amorphous forms. The ferric citrate complex is achiral.

Based on the review of data provided by the applicant, the CHMP considers that the ferric citrate coordination complex cannot be considered a new active substance on quality grounds.

Manufacture, characterisation and process controls

The active substance is manufactured in two synthetic steps from commercially available starting materials with acceptable specifications by two manufacturers. Both use essentially the same manufacturing process. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The active substance isolation conditions and subsequent milling step ensure that the required amorphous form of ferric citrate with high specific surface area and aqueous solubility is routinely produced. Re-processing may be performed if the active substance fails to meet specification for physicochemical properties or solvent or counter ion content. Potential and actual impurities were well discussed with regards to their origin and characterised. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in double polyethylene bags inside a HDPE pail or fibre drum, complete with desiccant which complies with the EC directive 202/2014 and EC 10/2011.

Specification

The active substance specification includes tests for appearance, identity (IR, colorimetric – Ph. Eur.), ferric iron assay (titrimetric), citrate content (HPLC), iron impurities (XRPD), ferrous iron content (titrimetric), chloride content (titrimetric), citrate impurities (HPLC), residual solvents (GC), water content (KF), acid insolubles

(gravimetric), trace metal impurities (ICP-MS and ICP-OES), particle size distribution (Ph. Eur.), Brunauer–Emmett–Teller (BET) specific surface area (Ph. Eur.) and microbial limits (Ph. Eur.).

Impurities are controlled below their respective permitted daily exposures (PDEs) in line with ICH guidelines Q3C and Q3D or by comparison to known safe levels in approved medicines.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. There is no Ph. Eur. reference standard against which the active substance can be calibrated. Therefore, the CHMP recommended conducting further characterisation of the ferric citrate reference standard and providing this information post-approval as soon as available.

Batch analysis data on 38 batches of the active substance manufactured on pilot to commercial scale are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on nine batches of active substance from one manufacturer and five batches from the other manufacturer stored in the intended commercial package for up to 36 months and for up to 24 months respectively, under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, assay, degradation products, water content and microbial quality. BET specific surface area was also monitored for the first 20 months of stability studies but since it did not change significantly and was well within specification, it was not tested at later time-points. No significant trends to any of the measured parameters were observed under either condition, indicating the physical and chemical stability of the active substance.

Photostability testing following the ICH guideline Q1B was performed on one batch. A slight increase in one impurity and significant loss of water was observed.

One batch was also exposed to stressed conditions at 60 ºC in open and closed bottles, dry, or at 75% RH. The dry samples showed significant loss of water and in increase in one impurity, the humid samples showed increases in multiple impurities and a loss of citric acid and did not fully dissolve. Degradation was investigated in acidic, basic and oxidative solutions. Precipitates formed in all cases and significant changes to ferric assay and impurities were observed under basic and oxidative conditions. The results show that the analytical methods used, the same as used for release, are stability indicating.

The stability results indicate that the active substance manufactured by the proposed manufacturers is sufficiently stable. The stability results justify the proposed retest period stored in the proposed container at 15-30 ºC.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The development of Fexeric focussed on keeping the dosage form as small as possible, given the high (1 g) dose of ferric citrate complex. Therefore, the content of excipients was kept as low as possible. Risk assessment was used to assess the impact of formulation and the manufacturing process on potential critical quality attributes such as dissolution rate and impurity profile, and thus, guide development activities.

The active substance is an amorphous solid with high specific surface area and is highly soluble in aqueous media. The physicochemical properties of the active substance are critical to its efficacy and need to be maintained during formulation. The amorphous nature also impacts its flow properties and agglomerates can

impact on content uniformity, challenges which were addressed by adopting a granulation approach. Excipients constitute only 10% by weight of the finished product and consist of a binder, lubricant, and film-coating. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Early studies used hard gelatin capsules. Other oral dosage forms were also investigated but film coated tablets were found to be the best option. The levels of excipients were modified during development to ensure a fast dissolution rate whilst maintaining processability of the blend following granulation. Tablets with a slightly different compositions were used in some phase III trials but these were later optimized for the commercial formulation. However, given the minor changes in formulation, the fact that the optimised formulation dissolves quicker and is more stable, and that the drug acts in the gut and is therefore not intended for absorption, no classical bridging bioequivalence study was required. Instead, a discriminatory dissolution method was developed which was able to distinguish between batches made with minor differences to composition, and with differences in manufacturing parameters. It is based on a pharmacopoeial method, using an EDTA solution which performs several functions: it simulates the pH of a fed stomach (4.6), slows dissolution relative to other acidic media, and forms an adduct with ferric ion which has a characteristic resolved UV absorption peak. The discriminatory power was adequately demonstrated.

The primary packaging is an HDPE bottle with child-resistant closure and desiccant. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: granulation of the screen-milled active substance and binder; blending with lubricant and compression; film-coating; packaging. The process is considered to be a standard manufacturing process. A validation protocol has been provided and the process will be validated on three successive production scale batches before commercialisation.

It has been demonstrated during development that the manufacturing process is capable of producing finished product of the intended quality in a reproducible manner. The in-process controls (IPCs) are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identification of iron and citrate (colorimetric and IR), assay of ferric iron (titrimetric), citrate content (HPLC), impurities (HPLC), ferrous iron content (titrimetric), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (KF) and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of finished product has been provided.

Batch analysis results are provided for more than forty batches manufactured on various scales from pilot to commercial confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Some early clinical batches had slightly different excipient levels but relevant parameters were in line with the specifications.

Stability of the product

Initially, stability data on four production scale batches of finished product, (containing active substance from both manufacturers), stored for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 12 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, ferric iron content, citrate content, impurities, water content, ferrous iron and dissolution. Out of specification results for dissolution were obtained on some batches on both long term and accelerated stability. Investigations revealed that an increase in water content was likely responsible and as such the level of desiccant was increased to protect against moisture uptake. These studies are considered supportive but not pivotal in determining shelf-life. There was no noticeable difference in stability of batches made with active substance from the different sources.

At the request of the CHMP, a new stability study using finished product packaged with an increased amount of desiccant was instigated during the procedure. Up to 6 months of data were provided under long term, intermediate and accelerated conditions showing all measured parameters within specifications and no significant trends. These studies will be continued up until shelf-life as per GMP requirements.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that Fexeric is not photosensitive.

Stability studies were carried on bulk tablets over a 12 month period under long term conditions and showed them to be stable for this period.

Finally, an in-use stability study was carried out using one batch of finished product stored at 25 ºC / 60% RH for up to 60 days. Bottles were opened and closed daily to simulate daily use. All tested parameters were within specification throughout the study and no significant trends were observed. In a parallel study, bottles were left completely open for up 60 days under the same conditions. All tested parameters were within specification after 60 days except for one lot which failed on dissolution. Based on this data, the proposed in-use shelf-life of 60 days is acceptable. However, CHMP recommends that the in-use stability study be repeated with a second batch of finished product towards the end of its shelf life as per the CPMP note for guidance on in-use stability testing of human medicinal products.

Based on available stability data, the shelf-life of 24 months not stored above 25 ºC and with the bottle tightly closed to protect from moisture as stated in the SmPC is acceptable.

Adventitious agents

The calcium stearate is of vegetable origin. No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on the development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate the consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- further characterisation of the ferric citrate reference standard should be conducted and information should be provided post-approval as soon as available;
- the long-term stability studies on batches of finished product with increased desiccant should be continued up to shelf-life and batches under intermediate conditions up to 12 months;
- the in-use stability study should be repeated with a second batch of finished product towards the end of its shelf life as per the CPMP note for guidance on in-use stability testing of human medicinal products.
- additional studies confirming the unique chemical structure of the coordination complex should be performed on a further 5 batches made using the commercial process and the results should be provided by August 2015. The data should include X-ray characterisation of the dinuclear species, quantification of the relative proportions of the claimed iron species ({$[Fe(H_2O)_6]^{3+}$} and $[Fe_2Citrate_2(H_2O)_2]^{2-}$), stability of the dinuclear complex at the relevant physiological pH (by studying the recoverability of the complex in solution through recrystallization) and mechanistic studies demonstrating the ligand exchange mechanism of the phosphate reaction by analysing the solid precipitate obtained by reacting the ferric citrate complex with phosphate in the presence of HCl.

2.3. Non-clinical aspects

2.3.1. Introduction

Fexeric (ferric citrate coordination complex, also referred to as KRX-0502, ferric citrate or JTT-751) is an oral iron-based phosphate binder. KRX-0502 reduces intestinal absorption of phosphate as ferric [Fe^{3+}] iron reacts with ingested phosphate to form an insoluble ferric phosphate complex in the gastrointestinal (GI) tract, which is excreted in the stool. As Fexeric is an iron-based phosphate binder, a small fraction (0.5% to 1%) of the iron is absorbed and assimilated into iron stores.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Because of the well-known properties of ferric, ferrous and citrate compounds, the non-clinical development of Fexeric was based on literature data, in compliance with ICH guideline M3(R2) and the Scientific Advice (EMA/CHMP/SAWP/261326/2011) received from the European Medicine Agency on 14 April 2011.

The primary pharmacological effects of JTT-751, i.e. lowering serum and urine phosphate levels have been demonstrated in vitro and in vivo PD studies in healthy and CKD rat model as reported in two published articles (Iida A et al., 2013 a and b). From bridging repeated dose toxicology studies in rat and dog there is confirmation of these findings as dose-related, statistically significant decreases in urinary phosphorus excretion were observed in the toxicity studies in rats and dogs. From in vitro PD study it can be seen KRX-0502 has certain affinity for phosphate over the acidic pH range, but in the neutral pH environment bounding capacity is expressed less. It would suggest that preparation binds phosphates stronger in stomach and at less extent in the intestines. 1 g of KRX-0502 can bind from 0.004 to 0.074 mg of phosphates depending on medium pH.

From in vivo data is evident that the effects of KRX-0502 and of ferric citrate are observed both in healthy rats and in rat models of chronic kidney disease; in this latter 1540 mg/kg/day of Fexeric in diet induced a reduction of -8 mg/dl serum Pi level following 1 week of treatment and this change was maintained after 21 and 35 days. Serum PHT was reduced as well as secondary effects of ectopic aorta calcification, hyperparathyroidism and bone abnormalities associated with chronic kidney disease.

In addition, information from the literature indicates that oral treatment with iron salts reduces the absorption of phosphorus in animal species other than rats and dogs.

Theoretically the citrate from KRX-0502 can reverse the metabolic acidosis associated with chronic kidney disease.

Fexeric ability to bind phosphorous was not compared to other known phosphorous-binding agents, approved for the treatment of hyperphosphatemia.

Secondary pharmacodynamic studies

Specific secondary pharmacodynamic studies were not conducted and reference is made to scientific literature stating that numerous ferric, ferrous, and citrate salts are approved as food supplements in the EU (Commission Regulation (EC), 2009). The published studies provided on animal models document the intestinal absorption of iron following oral treatment with ferric citrate (and other ferric compounds). Six of the seven toxicology studies performed in rat and dog included measurements of serum/plasma iron concentration, ferritin concentration, total iron binding Capacity (TIBC), and transferrin saturation (TSAT). The results are described in details in the PK section. Studies in beagle dogs (Nathanson, 1985) show that 4.5 ± 2.2% of the 2 mg dose of ferric citrate was absorbed under normal conditions (Tmax: 98 ± 10 min), increasing to 25.1 ± 8.1% in iron-deficient dogs (Tmax: 66 ± 16 min). Anaemia can lead to an acute four- to five-fold increase in iron absorption and plasma iron turnover. As iron stores become replete, decreases in iron absorption would be expected through well-established regulation mechanisms involving hepcidin (Valerio, 2007; Ganz and Nemeth, 2006).

Safety pharmacology programme

No dedicated safety pharmacology core battery study was performed with Fexeric on the basis of the known toxicity profile of iron and citrate and the lack of meaningful systemic exposure following a single dose.

The safety endpoints were evaluated through assessments performed during the repeat-dose toxicity studies (two in rats and two in dogs with KRX-0502; one in rats and one in dogs with JTT-751). Literature references documenting the effects of the ferric and of the ferrous ion were also supplied. The toxicological studies evaluated doses of KRX-0502 or JTT-751 in the range of 500-3500 mg/kg/day for durations of 4 to 32 weeks in rats and 400-2800 mg/kg/day for durations of 4 to 42 weeks in dogs. The corresponding HEDs were in the range of 81-565 mg/kg/day and 222-1556 mg/kg/day in rats and dogs respectively, equivalent to 0.4 to 2.8 and 1.1 to 7.8 times the MRHD of 200 mg/kg, respectively.

From the presented documentation no safety pharmacology effects have been identified except on the colour and consistence of stools during the KRX-0502 toxicology studies. Bibliographic data on the safety pharmacology of iron and of citrate report effects related to high levels of iron absorption on the CNS, including decreased brain levels of serotonin and dopamine, and altered behaviour and long term memory. No direct effects of iron on the ECG and blood pressure have been identified and a correlation between iron load and QTc is not clearly established. Citrate transiently decreases the QTc when administered IV, but not when given orally. The alkalinising effects of citrate are considered a secondary pharmacology effect in the indication of phosphate complexation in CKD patients. No safety pharmacology effects of oral iron and citrate formulations on the respiratory system were identified from the scientific literature.

Iron citrate does not modify duodenal motility *in vitro*. Prolonged oral administration of citrate has no effect on the skeletal system at a dose equivalent to the MRHD of KRX-0502. Systemic administration of citrate leads to a transient increase in bone turnover in healthy patients. However, beneficial effects of JTT-751 on the skeletal system have been demonstrated in rat model of chronic kidney disease.

2.3.3. Pharmacodynamic drug interactions

The complexing properties of iron suggest that KRX-0502 may interact with other orally co-administered drugs, resulting in a decrease in the absorption of the co-administered compound, possibly through the formation of a precipitate with the iron in the gastrointestinal lumen, and the excretion of the formed complex. Such interactions resulting from the properties of KRX-0502 could affect the pharmacokinetics of other drugs and are thus discussed under pharmacokinetic drug interactions.

2.3.4. Pharmacokinetics

Due to its main GI effect (iron-phosporous binding), standard PK studies which evaluate plasma concentration, Cmax, AUC and half-life of ferric citrate were not performed. However, since a part of iron and of citrate is absorbed from the GI following oral administration of Fexeric, TK data (serum iron, ferritin, TSAT, TIBC, UIBC) have been derived from the toxicology studies performed on rat and dog: one 4-week non-GLP study in rats, two GLP 90-day to 32-week duration studies in rats, one 4-week non-GLP study in dogs, and two GLP 16- to 42-week duration studies in dogs. The methods of analysis used and Validation procedures are considered adequate.
In rats, no changes in iron parameters occurred after 4 weeks treatment with KRX-0502 at doses up to 3 500 mg/kg. Serum iron and TSAT increased significantly in males after 13 weeks treatment at doses of 1400-2800 mg/kg/day, while this effect was noted in females after 33 weeks only. Serum iron and TSAT tended to return towards basal values for males at 33 weeks. Ferritin levels increased at doses of 2800 mg/kg/day in both sexes after 13 weeks treatment onwards, with increased values at 33 weeks compared to 13 weeks for both sexes.
In dogs, iron parameters were not affected after 4 weeks of treatment with doses of KRX-0502 of 500 or 1 000 mg/kg/day (N=1 for control, N=2 for treated groups). In studies of longer duration, increases in serum iron levels and TSAT occurred in both sexes at doses of 2 800 mg/kg/day for 16 weeks and 2 000 mg/kg for ≥ 29 weeks. Ferritin levels were increased time- and dose-dependently at doses of 1000 mg/kg/day for 42 weeks and 2000 mg/kg/day for ≥ 16 weeks in males and 400 mg/kg/day for 42 weeks; 1000 mg/kg/day for ≥ 29 weeks; ≥ 2000 mg/kg/day for ≥ 16 weeks in females.
Pharmacokinetic parameters of iron and of citrate absorption following oral administration of ferric citrate are sparsely described in the literature. Iron absorption in rats peaked at less than 0.5% of a 0.5 mg dose 1 hour after administration. Plasma iron levels in dogs peaked at less than 5% of a dose of 2 mg ferric citrate 98 min after treatment in normal animals, increasing to 25% after 66 min in iron-deficient dogs. In comparison, iron

retained in humans 2 weeks after oral administration of 100 mg iron as ferric citrate to an empty stomach was 1.58% of the initial dose.
Absorption is affected by dietary ingredients, although the magnitude of the effect depends on study design and duration. In a single-meal study, mean group absorption ranged from 6.1% for volunteers taking a standard diet, to 2.3% when absorption inhibitors are present in the diet, to 13.5% when the diet included absorption enhancers. However, in a 2-week study, when homeostatic regulatory mechanisms can influence uptake from the GI tract, mean absorption ranged from 6.1% for volunteers taking standard meals to 3.2% when absorption inhibitors are present in the diet, to 8.0% when the diet included absorption enhancers.
Citrate is present in low concentrations in circulation and is excreted rapidly upon exogenous administration. In humans, plasma concentrations are approximately 0.1 mM (18.9 µg/mL). In the dog, reported citrate concentrations, measured in whole blood, range from 9 to 19 µg/mL; while in rabbits citrate concentrations, measured in serum, are reported to be higher (70 to 140 µg/mL). Citrate is quickly absorbed following oral administration to humans, peaking at 30 min. Data suggests that normal circulating citrate concentrations are relatively independent of normal dietary citrate intake; however, plasma and urine citrate levels increase following oral doses in the range of about 8.6 to 55 mEq citric acid or potassium citrate.
Literature data show that iron in the blood is bound to transferrin, which protects the body from the oxidative properties of iron. Serum iron (ie, iron bound to transferrin) represents only a very small proportion of total body iron (about 0.1%). About 45% to 70% of iron is found in the erythrocytes within haemoglobin. Another 7.5% to 15% is found in myoglobin in the muscles, in a variety of different enzymes ("haem" and "non-haem"), and in storage form. Iron-requiring cells, primarily cells in the bone marrow involved in erythropoiesis and liver cells have membrane-bound transferrin receptors by which iron is transported into the cell. Most stored iron is in the form of ferritin, found in the liver, bone marrow, spleen, and muscles. Such iron distribution pattern is confirmed by the histopathological assessments performed during the toxicology studies performed with KRX-0502/JTT-751 in rats and dogs. Following chronic treatment with ferric citrate, iron deposition was observed in the gastro-intestinal tract, the liver, spleen, kidney, lymph nodes and to a lesser extent, ovaries, pancreas, heart and lungs.
In the mouse, 70% of citrate in the body is localized in the bone; while soft tissues do not contain appreciable stores of citrate.
No metabolism study was performed since metabolism of iron and citrate is well established.
Physiologically iron that is absorbed is largely conserved; mammals have no physiologic process for iron excretion. Iron losses are small and can occur through skin exfoliation, sloughing off of intestinal cells, menstruation in females, and minimally through biliary and urinary excretion (as reviewed by Geisser, 2011). Iron loss also occurs with haemodialysis. Oral potassium citrate at doses of 30 to 100 mEq/day (3.24 g/day to 10.8 g/day) is used for the treatment of kidney stones, including those associated with hypocitraturia and unduly acidic urine pH (Hall, 2009,Pak, 1994). Upon exogenous administration, citrate is excreted rapidly through the lungs as CO2 and the kidney (80% to 90% of an i.v. dose within 3 hours).

The DDI programme evaluated the in vitro and in vivo (healthy volunteers - see clinical section) interaction of KRX-0502 and the main classes of drug potentially co-administered with it to patients with CKD.

Based on the in vitro visual observation of precipitate occurrence when KRX-0502 is mixed with the drugs, the studies indicate that DDI is likely to occur with drugs of the following classes: antibiotics, anticonvulsant, antidepressant, anti-osteoporosis, anti-parkinsonian and immunosuppressive drugs.
The HPLC results generally confirmed those obtained by visual observation and confirmed the interaction of KRX-0502 with cefdinir, ciprofloxacin, doxycyclin and its absence with levofloxacin and vancomycin for antibiotics, as well as the absence of interaction between KRX-0502 and the tested drugs from the following

classes: anticoagulants, antidiabetics, anti-hyperlipidemics, treatments of cardiovascular diseases and vitamin D analogues.

2.3.5. Toxicology

Due to the fact that the properties of both moieties of KRX-0502, iron and citrate are well established, the KRX-0502 non-clinical program relied on seven repeated toxicity studies in rats and dogs and on the existing scientific literature. Information pertaining to acute toxicity, genotoxicity, carcinogenicity, and reproductive toxicity can be found in the published literature for the individual components in the drug substance, iron and citrate.

Single dose toxicity

The acute toxicity of ferric citrate has not been evaluated by the applicant. However, acute toxicity following oral administration of other iron-containing compounds and citrate, the two components in ferric citrate, are available in the published literature. The LD_{50} for ferrous iron are reported to range from 31.5 to 630 mg/kg, 255 to 2329 mg/kg and 464 to 600 mg/kg in mice, rats and dogs, respectively. LD_{50} in fasted animals (31.5 to 42.5 mg/kg [mice]; 255 mg/kg [rats]) are much lower compared to LD_{50} in fed (305 to 516 mg/kg [mice]; 865 to 2329 mg/kg [rats]) animals. Mice appear to be more sensitive than rats to large single doses of ferrous salts, as demonstrated by the lower LD_{50} values observed in mice compared to rats. Acute toxic effects that have been described in animals exposed to lethal doses of iron include decreased activity, weakness, decreased muscular control, prostration, urination, bowel obstruction, gastroenteritis (including diarrhea and vomiting leading to dehydration, haemoconcentration and electrolyte imbalance), rapid and shallow respiration, convulsions, coma, respiratory failure and cardiac arrest. Post-mortem examination reveals congestion and hemorrhagic necrosis of the GIT. Citric acid has a low acute toxicity when administered orally to mice (LD50=5.4 g/kg) and rats (LD_{50}=3 to 12 g/kg); these doses are associated with acidosis and calcium deficiency. “High” (unspecified) doses of citric acid have also been reported to cause nervous system effects as well as severe damage to the stomach mucosa.

Repeat dose toxicity

KRX-0502 was tested via dietary administration in repeat-dose toxicity studies in rats (28 days, 90 days and 32 weeks) and dogs (28 days, 33 days, 16 weeks and 42 weeks). The main target organ of KRX-0502 was the GIT, where black material identified as being related to the test article was observed, together with dose related appearance of this material in macrophages, associated with GIT erosion and inflammation. Test article-related effects included a decrease in body weight and increased food intake, changes in serum iron parameters consistent with increased iron absorption, increased liver weight with signs of alteration of the liver function evidenced by an increase in liver enzyme and decreased albumin levels. These changes were associated with chronic inflammation foci and bile duct hyperplasia. Discoloration occurred in mediastinal and mesenteric lymph nodes together with accumulation of brown pigment in macrophages, sinus ectasia/cysts in rats. One male dog receiving 2000 mg/kg/day was euthanized in week 40 for poor condition that was considered to be due to test-article related liver toxicity, as assessed by standard clinical chemistry, including iron parameters, and microscopic pathology. Reversibly decreased serum and urine phosphorus levels occurred, together with increased urinary pH and calcium excretion as well as decreased PTH levels in rats.

The NOAEL was determined to be 2800 mg/kg in rats when ferric citrate was orally administered for up to 32 weeks and the NOAEL in dogs was considered to be 400 mg/kg/day when ferric citrate was orally administered for up to 42 weeks. This corresponds to a safety margin of 2.25 for rats and 1.1 for dogs.

Genotoxicity

No genotoxic potential was evidenced for ferric citrate in a bacterial reverse mutation test and a chromosomal aberration test in Chinese hamster fibroblasts. A number of *in vitro* and *in vivo* genotoxicity studies have been reported for various iron containing compounds and for citric acid as well. Results from *in vivo* genotoxicity studies are more relevant than those from *in vitro* studies since iron is not presented to cells in a free state (unbound to transferrin) in the body, as it is in the *in vitro* studies. Out of twelve compounds with published genotoxicity studies, none of the ferric compounds were positive in the bacterial reverse mutation test and three out of five ferrous compounds tested (ferrous sulphate, ferrous fumarate and ferrous gluconate), which were initially found positive were changed for ferric orthophosphate (equivocal), ferrous sulphate (inconclusive) and ferrous fumarate (positive). Ferrous lactate and ferrous sulphate were also positive in *in vitro* chromosomal aberration tests. Ferrous sulphate and iron dichloride were evaluated in *in vivo* micronucleus tests in mice and were found negative. In one additional study testing ferrous sulphate, chromosomal aberrations were observed in bone marrow cells following administration of ferrous sulphate to rats via intraperitoneal administration. In *in vivo* tests, oral administration of ferric chloride and ferrous sulphate did not induce micronuclei in stomach, duodenum and colon of mice, either fasted or fed. However, a dose related increase in nuclear aberrations was observed in the colon. In studies evaluating iron salts administered intraperitoneally to rats or mice, two out of three studies did not evidence increased bone marrow micronuclei and one study showed that ferrous sulphate induced chromosomal aberrations in rat bone marrow cells. The *in vitro* studies evaluating the potential genotoxicity of citric acid were negative.

Carcinogenicity

The evaluation of the chronic inflammatory effects of KRX-0502 in the chronic toxicity studies in rats and dogs indicates that low intensity inflammation of the GIT occurs dose dependently in rats only during the 33-week treatment with KRX-0502. The low intensity and partial recovery of this effect within 1 month, as well as the absence of reported lesions and neoplasms indicates a low carcinogenic potential of KRX-0502 in the GIT of chronically treated animals. This observation is confirmed by literature results from testing ferric and ferrous compounds in lifetime studies. Although the doses tested were limited by the toxicity of the compounds under the conditions tested, the studies were conducted at the experimentally determined MTDs, and no carcinogenic effects of these iron compounds were found. A safety evaluation of patients enrolled in the studies with KRX-0502 did not indicate any carcinogenic potential of KRX-0502 during the evaluation period of up to 2 years. In patients with haemochromatosis, the risk of cancer has been documented from increased hepatic cancer incidence, likely associated with the absence of homeostatic regulation of iron absorption, which results in increased absorption of iron, leading eventually to iron overload.

Therefore, the risk of cancer in patients treated orally with KRX-0502 should be minimized by the homeostatic mechanisms which control iron absorption from the GI lumen, by the loss of iron that accompanies dialysis, by the frequent monitoring of patients on dialysis and by the fact that treatment with KRX-0502 will be contraindicated in patients with haemochromatosis.

Reproduction Toxicity

An evaluation of the reproductive organs from animals tested in the repeated dose toxicity studies did not provide evidence of any effects impairing the fertility of both males and females and the observed NOAEL for these effects was 2.25 and 5.56 times the MRHD of KRX-0502 in rats and dogs, respectively. Studies of other iron-containing compounds and citric acid have not shown any effects on fertility, embryonic and embryofoetal development at the highest oral doses tested to mice, rats, and rabbits. In the reproductive toxicology studies, none of the highest doses tested led to maternal toxicity, indicating that the NOAELs to dams as well as the safety indexes are likely to be higher.

Toxicokinetic data

Toxicokinetic data (i.e., plasma Cmax, AUC and half-life) were not measured, as traditional pharmacokinetic parameters are not relevant to the measurement of total body exposure to iron. This is because free iron is toxic to cells and does not circulate freely in the body; instead, it is bound by specific proteins that facilitate its transport and storage. Thus, total body exposure to iron is more accurately estimated by measurement of parameters associated with changes in iron transport and storage proteins. These parameters include serum iron, transferrin saturation (TSAT), ferritin, total iron binding capacity (TIBC) and unsaturated iron binding capacity (UIBC).Monitoring of iron parameters (serum iron, TSAT, ferritin, and TIBC) during the toxicology studies indicated that no changes in iron levels occurred during daily administration for 28 days at doses up to 2800 mg/kg/day in the rat, and 1 000 mg/kg/day in the dog.

Local Tolerance

Local tolerance to ferric citrate was documented by macroscopic and microscopic evaluation of the GI tract of animals during the repeated dose toxicology studies; therefore no separate local tolerance studies have been conducted. KRX-0502 is administered orally and the outcome of the repeated dose toxicity studies indicates that it is well tolerated in the GIT.

Other toxicity studies

- Immunotoxicology: On the basis of the evaluation of the effects of ferric citrate on the organs from the reticuloendothelial system and on the haematology of treated rats and dogs during the repeated dose toxicology studies, no immunotoxic effects of ferric citrate are anticipated. Increased serum neutrophils and eosinophils noted in rats, as well as accumulation of brown pigmented macrophages in all organs of the RES and changes in lymph nodes at after 32 weeks in rats were attributed to iron absorption.
- Photo toxicity: Based on the outcome of the chronic toxicity studies in rats and dogs and on the published literature, the potential for phototoxicity of KRX-0502 is considered low.

2.3.6. Ecotoxicity / environmental risk assessment

The active substance KRX-0502 or ferric citrate is dissociated in the ferric ion and the citrate ion that are ubiquitously present in the environment. Their environmental toxicity is well documented. Considering the above data, KRX-0502 is not expected to pose a risk to the environment.

2.3.7. Discussion on non-clinical aspects

The non-clinical development programme of Fexeric was based on published data on several iron salts and Fexeric, and on 7 dose-repeated toxicity studies newly submitted in this MAA. The mode of action was demonstrated in vitro even if no comparison with other phosphate-binders (Al, Ca, etc.) has been made in terms of binding capacity/efficiency. Pharmacological activity in reducing serum Pi levels was demonstrated in a rat CKD model. Safety pharmacology studies were not performed; toxicity data on target organs were retrieved by the toxicology studies except for cardiovascular system for which literature of clinical use was reported. Due to the effect in gastro intestinal tract, no standard PK/TK studies were performed; change in iron parameters (serum iron, ferritin, etc.) were measured in toxicology studies as some amount of iron from the hydrolysis in the lumen is absorbed. Results from in vitro DDI studies showed interaction of KRX-0502 with cefdinir, ciprofloxacin, doxycyclin and no interaction with levofloxacin,vancomycin, as well several medicinal products from the following classes: anticoagulents, antidiabetics, anti-hyperlipidemics, treatments of cardiovascular

diseases and vitamin D analogues. Toxicity studies do not reveal particular concerns with a NOAELs that in rat and dog are very low. No studies on carcinogenic potential nor on reproductive embryofoetal toxicity were performed; published data do not indicate a potential risk. Three juvenile rat toxicology studies are currently planned as part of the Paediatric Investigational Plan.

2.3.8. Conclusion on the non-clinical aspects

The non-clinical data are considered appropriate to support the proposed clinical use of Fexeric for control of hyperphosphatemia in adult patients with CKD.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. Tabular overview of clinical studies

KRX-0502 was assessed clinically during 18 completed studies in the KRX-0502 development programme (15 studies in CKD 5D; 3 studies in CKD ND Table 2).

Table 2: Overview of Fexeric Clinical Programme

Study	Study Design	Population	Number of Subjects	Datasets	
Completed Studies in dialysis patients					
Study GBA2-1 Phase 2 Japan	Randomized, double-blind, parallel, comparative, dose-response study to determine the effect of JTT-751 at doses of 1.5, 3, and 6 g/day and Placebo for 28 days.	Subjects with CKD on haemodialysis	Randomized: 192 Dosed Placebo : 48 JTT-751 1.5 g/day: 49 3.0 g/day: 50 6.0 g/day: 45	Dose-finding Dialysis Studies	Safety Evaluation
KRX-0502-305 Phase 3 US	Multicenter, randomized, open-label, dose-ranging, efficacy trial to determine the dose-response relationship and the efficacy of a fixed dose of 1, 6, and 8 g/day of KRX-0502 over 4 weeks.	Subjects with CKD on haemodialysis	Randomized/dosed: 154/151 KRX-0502: 1 g/day: 51 6 g/day: 52 8 g/day: 48		Pooled Safety Set for Safety Evaluation (PSS)
PBB00101 Phase 2 US/Taiwan	Randomized, double-blind, Placebo-controlled, dose-ranging study to determine the effect of ferric citrate at doses of 2, 4, and 6 g/day for 28 days.	Subjects with CKD on haemodialysis	Randomized: 116 Dosed Placebo: 16 Ferric citrate: 2 g/day: 33 4 g/day: 34 6 g/day: 33		
KRX-0502-304 Phase 3 US/Israel	58-week, three-period, multicenter, randomized, open-label, active-controlled* then Placebo-controlled trial efficacy & safety study. Starting dose of KRX-0502: 6 g/day Dose titrated to max. dose of 12 g/day to maintain serum phosphorus (P) between 3.5 and 5.5 mg/dL. *Active control: sevelamer carbonate, calcium acetate, or both	Subjects with CKD on dialysis	Randomized/dosed: 441/438 Safety Assessment Period KRX-0502: 292/289 Active control: 149/149 Efficacy Assessment Period: KRX-0502: 96/95 Placebo: 96/95	Long-term efficacy studies	PSS
Study GBA4-5 Phase 3 Japan	Multicenter, uncontrolled, open-label study to determine the long-term safety and efficacy of JTT-751. Treatment duration: up to 28 weeks Starting dose of 1.5 g/day titrated up to 6.0 g/day to maintain serum P between 3.5 and 6.0 mg/dL.	Subjects with CKD on haemodialysis	Enrolled: 235 Dosed: 234		Safety Evaluation
Study GBA4-3 Phase 3 Japan	Multicenter, uncontrolled, open label safety & efficacy study Treatment duration: 12 weeks + 40 weeks in extension study Starting dose of 1.5 g/day of JTT-751, titrated to max. dose of 6 g/day maintain serum P between 3.5 and 5.5 mg/dL.	Subjects with CKD on peritoneal dialysis	Dosed: 56 (19 in extension study)	Long-term efficacy studies	Safety Evaluation

Study	Study Design	Population	Number of Subjects	Datasets	
Study GBA4-6 Phase 3 Japan`	Multicenter, uncontrolled, open-label, study to determine long-term safety and efficacy of of JTT-751. Treatment duration: 52 weeks Starting doses between 1.5 and 6.0 g/day, titrated to maintain serum P between 3.5 and 6.0 mg/dL.	Subjects with CKD on haemodialysis	Enrolled: 180 Dosed: 180		
KRX-0502-201 Phase 2 US	Multicenter, open-label study to determine the safety and tolerability of KRX-0502 over 4 weeks. Starting dose of ≈4.5 or ≈6.0 g/day Dose titrated to max. dose of 11.3 g/day to maintain serum P between 3.5 and 5.5 mg/dL.	Subjects with CKD on haemodialysis	Enrolled/dosed: 65/55 4.5 g/day: 34 6.0 g/day: 21		
KRX-0502-202 Phase 2 Israel	Uncontrolled, open-label study to assess a new formulation of KRX-0502 (1-g caplet) for efficacy and tolerability over 28 days. Starting dose of 6 g/day of KRX-0502, titrated to max. dose of 12 g/day to maintain serum P between 3.5 and 5.5 mg/dL.	Subjects with CKD on haemodialysis	Enrolled: 22 Dosed: 22	**Efficacy Evaluation**	
Study GBA2-2 Phase 2 Japan	Open-label study To explore the safety and efficacy of a fixed dose of 7.5 or 9 g/day of JTT-751 in HD subjects over 14 days.	Subjects with CKD on haemodialysis	Enrolled: 10 Dosed: 10 (at 7.5 g/day; 9 g was not administered in the study)		
Study GBA4-1 Phase 3 Japan	Multicenter, randomized, open-label, active-controlled, parallel-group study to evaluate the safety and efficacy of JTT-751 compared with sevelamer hydrochloride over 12 weeks. Starting dose of either 1.5 g/day of JTT-751 or 3 or 6 g/day of sevelamer, titrated to maintain serum P between 3.5 and 6.0 mg/dL.	Subjects with CKD on haemodialysis	Randomized: 229 Dosed JTT-751: 116 Sevelamer hydrochloride: 113		**Safety Evaluation**
Study OLE PBB00101 Phase 2	Compassionate use, uncontrolled, open-label, safety extension study of PBB00101 to examine long-term safety of KRX-0502. Treatment duration: up to 1 year Maximum dose: 6 g/day of KRX-0502	Subjects with CKD on dialysis. Subjects completing Phase 2 Study PBB00101 were admitted into the open-label study.	Enrolled: 29 Dosed: 28		
Univ. of Michigan Study 1 Phase 1/US	Open-label, crossover, comparative study To examine the safety, tolerability, and efficacy of ferric citrate (3 g/day) compared with calcium carbonate (3 g/day) over 28 days.	Subjects with CKD on haemodialysis	Enrolled: 54 Dosed: 54 All subjects exposed to both treatments		**Safety Evaluation**
Univ. of Michigan Study 2 Phase 2a/US	Randomized, open-label, active control study To examine the safety, tolerability, and efficacy of ferric citrate (4.5 g/day) compared with calcium acetate (4 g/day) over 28 days.	Subjects with CKD on haemodialysis	Randomized: 28 Dosed Ferric citrate: 14 Calcium acetate: 14		

Study	Study Design	Population	Number of Subjects	Datasets	
KRX-0502-307 Phase 3 US	Uncontrolled, open-label, safety extension of Study 304 to evaluate the long-term safety of KRX-0502. Treatment duration: up to 48 weeks Maximum dose: 12 g/day of KRX-0502 Subjects who completed the SP and, if eligible, the EAP of Study 304 could enter the extension study and receive KRX-0502 titrated to maintain serum P between 3.5 and 5.5 mg/dL.	Subjects with CKD on dialysis Subjects completing Phase 3 Study 304 were admitted into the open-label study.	Enrolled: 168 Dosed (All KRX-0502): 166		Long-term safety extension study
Completed Studies in non-dialysis patients					
KRX-0502-204 Phase 2 US	Multicenter, randomized, double-blind, Placebo-controlled, 3-period study safety & efficacy study. Treatment duration: up to 12 weeks Starting dose of either Placebo or 3 g/day of KRX-0502, titrated to a max. dose of 12 g/day to maintain serum P between 3.0 and 3.5 mg/dL.	Subjects with CKD not on dialysis	Randomized: 149	Non-dialysis efficacy studies	Non-dialysis Studies for Safety
Study GBA4-4 Phase 3 Japan	Randomized, double-blind, Placebo-controlled, comparative study to determine the efficacy and safety of JTT-751 over 12 weeks. Starting dose of 1.5 g/day of JTT-751 or Placebo; dose was titrated to a max. dose of 6 g/day to maintain serum P between 2.5 and 4.5 mg/dL.	Subjects with CKD not on dialysis.	Randomized: 89 Dosed JTT-751: 59 Placebo: 30		
Study GBA4-7 Phase 3 Japan	Multicenter, uncontrolled, open-label extension study to GBA4-4 to determine the safety and efficacy of long-term administration of JTT-751. Treatment duration: 40 weeks (52 weeks total including prior study) Subjects were treated with JTT-751 for up to an additional 40 weeks (total of 52 weeks) with doses ranging between 1.5 and 6.0 g/day of JTT-751, titrated to maintain serum P between 2.5 and 4.5 mg/dL.	Subjects with CKD not on dialysis. Subjects completing Phase 3 Study GBA4-4 were admitted into the open-label study.	Enrolled: 29 Dosed: 29		

2.4.2. Pharmacokinetics

Changes in iron parameters (PD marker) subsequent to treatment with KRX were assessed during all 17 completed studies in the KRX-0502 development programme (14 studies in CKD 5D; 3 studies in CKD ND.

To assess iron absorption and systemic exposure standard validated methods were used to measure the iron parameters (iron concentration, ferritin concentration, UIBC, TIBC, and TSAT) at the contract laboratory performing the toxicology studies (Huntingdon Life Sciences [HLS], East Millstone, NJ).

Validation procedures for serum iron included assessments of precision, linearity, accuracy, sample stability, and bias (method comparison). Validation procedures for serum ferritin and UIBC included assessments of precision, linearity, accuracy, and sample stability. Given that the phosphate binding effect of KRX-0502 is not dependent on the systemic availability of ferric citrate, conventional pharmacokinetic studies are not relevant

for understanding this primary pharmacodynamic effect of KRX-0502. A fraction of the ferric iron that is not involved in phosphate binding, is absorbed from the GI tract, principally after reduction to the ferrous form. Conventional plasma protein binding studies were not conducted with KRX-0502 given that ferric citrate is not systemically absorbed.

Bioavailability of KRX-0502 iron component

Calculation of mean daily dose for 52 week period

For Study 304, the mean daily dose of KRX-0502 for the 52 week treatment period was 6.21 g/day. The population selected for calculating the bioavailability of iron absorbed corresponded to “Subjects having completed the Safety Assessment Period on Study Drug (304 patients overall). This population was restricted to patients having data from visits 4, 11 and 21 (Baseline, Week 12 and Week 52)". In order to estimate the bioavailability of iron from KRX-0502, only those patients who did not receive IV iron were selected for the calculation. A total of 26 patients who completed the Safety Assessment Period on Study Drug (KRX-0502), had data from visits 4, 11 and 21, and received no IV iron. Exposure and drug accountability data were extracted from Study 304 CSR. Since the dose ofKRX-0502 was titrated and thus changed during the study period, the average number of tablets taken daily was calculated for the number of days elapsed between the Visit 5 Start Date and the Visit 21 Stop Date for each of the 26 patients. The “Mean daily dose (tablets)”, as well as the change from baseline in serum iron and ferritin were further calculated as the average ± SD of the individual data for the 26 selected patients.

Calculation of mean daily dose for 12 week period

The mean daily dose of KRX-0502 during the first 12 weeks of Study 304 in those subjects who did not receive IV iron was 6.39 ± 2.4 g/day (n=35). The calculated bioavailability of iron from KRX-0502 based on the average daily dose and change in serum iron over 12 weeks was 0.7%, similar to the value calculated using the population who completed 52 weeks of treatment (0.8%). The calculated bioavailability of iron from KRX-0502 based on the average daily dose and change in serum ferritin over 12 weeks was 0.61%, similar to the value calculated using the population that completed 52 weeks of treatment (0.67%). Studies investigating the extent of food effects on bioavailability were not conducted as the influence of food on iron absorption is well known. KRX-0502 must be taken with food for its phosphate-binding effect and subjects in all clinical studies received KRX-0502 together with meals, as reflected in the product information. In the absence of studies investigating the effect of food on the bioavailability of KRX-0502, a summary of studies form literature on this topic were presented. This is considered acceptable.

Distribution

No formal biodistribution studies were performed for KRX, assuming very limited absorption of iron from KRX. This is endorsed.

Elimination

No elimination studies have been performed but ferric citrate forms an insoluble complex with dietary phosphate, which is not absorbed or metabolised during GI transit and is excreted in the faeces. This is considered acceptable.

Dose proportionality and time dependencies

No dose proportionality PK studies were performed. This is acceptable considering the low assumed bioavailability extent. No time dependency PK studies were performed. This is acceptable considering the low assumed bioavailability extent.

Special populations

No dedicated PK study in special population was performed with Fexeric. All PK data were derived from pivotal studies that were carried out in patients with chronic kidney disease: from dialyzed patients in study 304 and from non dialysed patients in study 204. Fexeric has been administered to over 400 patients ≥ 65 years of age in studies where the dose was titrated to achieve target serum phosphorus levels. The elderly were treated according to the recommended dosing regimen without any safety concerns. Hence, section 4.2 of SmPC informs the treating physician that information for hepatically impaired patients and on elderly patients (> 75 years of age) treated with Fexeric is limited.

Pharmacokinetic interaction studies

Effects of other medicinal products on Fexeric: The subgroup analysis from pivotal study 304 did not reveal any change in terms of serum Pi, TSAT, and ferritin levels when Fexeric is taken with a number of frequently co-prescribed medications: fluoroquinolones, tetracyclines, proton pump inhibitors, thyroid hormones, sertraline, Vitamin D, warfarin, acetylsalicilic acid.

Effects of Fexeric on other medicinal product: Drug-drug interaction studies conducted in healthy male and female subjects confirms the potential of KRX-0502 to interact with ciprofloxacin (decreased bioavailability [AUC] by approximately 45%) and no interaction with clopidogrel (anticoagulant), glimepiride (antidiabetic), losartan, diltiazem and digoxin (treatments of cardiovascular diseases). Drug-drug interaction of ferrous sulphate and thyroxin has been investigated by Campbell et al., 1992 that showed that simultaneous ingestion of ferrous sulphate and thyroxin causes a variable reduction in thyroxin efficacy in patients with primary hypothyroidism, which is clinically significant in some patients. From in vitro studies, certain antibiotic (doxycycline, cefdinir), anticonvulsant (valproate sodium), antidepressant (sertraline HCl), bisphosphonate (alendronate sodium), anti-parkinsonian (levodopa) and immunosuppressant (methotrexate) medications showed the potential to interact with Fexeric: any of these or other medicinal products which bioavailability could be affected by Fexeric, should be taken at least 2 hours before or after Fexeric. Fexeric should not be administered with aluminium compounds because citrate is known to increase aluminium absorption.

2.4.3. Pharmacodynamics

Mechanism of action

The KRX is a calcium-free phosphate binder. It has multiple effects in humans as it was concluded by non-clinical studies: (1) to lower inorganic phosphorus serum levels and (2) to improve iron status in CKD ND and CKD 5D patients. No formal studies were performed to test the mechanism of action; no primary PD studies were performed to assess the phosphate binding capacities in clinical setting. This is considered acceptable. The non-clinical investigations showed that KRX as in case of all phosphate binders works through the same mechanism of action i.e. formation of insoluble complex with dietary phosphate that are then eliminated in the faeces.

Primary and Secondary pharmacology

Serum phosphorus (P) was assayed as a primary efficacy parameter in all clinical studies. Three studies examined the dose-response relationship of various ferric citrate formulations, including KRX (in study 305, Table 5) by administration of fixed doses ranging from 1 to 8 g/day for 4 weeks. The dose-response relationship was confirmed for treatment with 1, 6, and 8 g/day of KRX-0502 for 28 days by a regression analysis ($p<0.0001$).

Table 3: Change From Baseline to End of Treatment Period (Week 4) in serum P in study 305 (Efficacy Analysis Population)

	KRX-0502 1 g/day	KRX-0502 6 g/day	KRX-0502 8 g/day
n	50	51	45
Mean (SD) at baseline	7.33 (1.737)	7.56 (1.727)	7.47 (1.631)
n	38	44	34
Mean (SD) at the end of treatment[a]	6.66 (1.078)	5.61 (1.545)	5.44 (1.528)
Mean (SD) change from baseline	**-0.10** (1.285)	**-1.86** (1.692)	**-2.13** (1.998)
Comparison with 1 g/day[b]	NAP	**-1.52** (-1.98, -1.07) <0.0001	**-1.94** (-2.41, -1.46) <0.0001
Comparison with 6 g/day[b]	NAP		**-0.41** (-0.88, 0.06) 0.0856

[a] *End of treatment was denoted as Week 4.*

[b] *KRX-0502 (1, 6, and 8 g/day) pairwise compared with each other, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and p-value for testing mean difference equal to 0.*

CI=confidence interval; n= number of subjects for whom data available; NAP=not applicable; SD=standard deviation.

The primary PD investigations employed various formulations of ferric citrate (including KRX) and various dosages (ranging from 1 to 8 grams/day) comparing to placebo. Absolute effect was shown as through dose dependent decrease in serum P levels from baseline to Week 4:

	Ferric Citrate	JTT-751	KRX
Placebo	-0.1	0.04	NA
1- 1.5 -2 g/day	-0.3 (2g/d)	-1.28 (1.5 g/d)	-0.10 (1 g /d)
3.0 g/day	-1.1	-2.16	
6.0 g/day	-1.5	-4.10	-1.86
8.0 g/day			-2.13

Secondary pharmacology

The secondary pharmacology was assessed by testing changes in iron metabolism. Iron parameters provide a direct measure of bioavailability and secondary PD (in terms of incorporation into iron stores). Iron status was monitored in all studies across the clinical programme, including all studies, which contributed to the efficacy evaluation. Studies of KRX-0502 and JTT-751 in CKD ND and 5D showed an increase with dose and time in serum iron, ferritin and TSAT levels, and a decrease in mean TIBC levels, consistent with increase in iron stores.

Overall, changes in iron parameters were first observed within the first 4 weeks of administration. In the longer-term studies, TSAT values reached a plateau by approximately Week 12, and ferritin levels plateaued by approximately Week 24. In both, dialysis (Study GBA2-1) and non-dialysis (Studies 204 and GBA4-4) studies, changes from baseline to end of treatment in all iron parameters were of a greater magnitude in the ferric citrate-treated groups compared to the placebo groups. In Study GBA2-1, all treatment groups that received JTT-751 achieved a significant increase in ferritin vs. placebo group ($p<0.0001$); all groups that received JTT-751 at a dose of ≥3 g/day showed statistically significant increases in serum iron and vs. placebo group. All JTT-751 groups showed a significant decrease in TIBC vs. placebo group. In Study 204, in CKD ND subjects with iron deficiency anaemia who did not receive concomitant IV iron/ESA administration, treatment with KRX-0502 for 12 weeks resulted in significant improvements in TSAT (co-primary endpoint), ferritin, Hgb, serum iron and TIBC relative to the placebo group ($p<0.001$ for treatment difference for each parameter). In Study GBA4-4, subjects who received JTT-751 (1.5 g/day titrated up to 6 g/day) had significantly increased levels of serum iron, ferritin and TSAT and decreased levels of TIBC at end of treatment vs. placebo group. These increase in iron parameters were sustained in the extension study (Study GBA4-7) for an additional 40 weeks of treatment.

2.4.4. Discussion on clinical pharmacology

The non-clinical development programme showed that orally administered KRX-0502 is a specially designed ferric (Fe^{3+}) phosphate complex that reacts with dietary phosphate in the GI tract, precipitating phosphate as ferric phosphate, an insoluble complex which is not absorbed or metabolised during GI transit and is excreted in the faeces. The citrate moiety released from the KRX complex is absorbed and subsequently converted to bicarbonate in the tissues, or excreted in the urine.

The applicant did not perform conventional clinical pharmacology programme and based the programme on the facts that

(1) direct pharmacodynamic measure of the phosphate binding effect is the change in serum phosphorus levels, an objective clinical endpoint assessed in all clinical studies;

(2) the phosphate binding effect of KRX-0502 is non-systemic and not dependent on the systemic availability of ferric citrate;

(3) the iron component absorbed is not metabolised, but used for biosynthesis, stored in iron stores or excreted.

Overall, the PK is considered appropriate to support the proposed clinical use of Fexeric for control of hyperphosphataemia in adult patients with chronic kidney disease. The non-clinically proven mechanism of action (increases faecal excretion of P, decreased plasma and urine P levels) are relevant to clinical setting. Clinical studies showed that KRX reduces P in plasma in CKD at both non dialysis and dialysis population. No dedicated PD interaction studies were performed.

2.4.5. Conclusions on clinical pharmacology

The pharmacological profile of Fexeric is considered sufficiently characterised.

2.5. Clinical efficacy

2.5.1. Dose response studies

Study 305 was a phase 3, 6-week, multicentre, randomised, open-label, dose-ranging study conducted in US to determine safety and efficacy of KRX-0502 at doses 1, 6 and 8 g/day. This study evaluated change from baseline to Day 28 in serum Pi concentrations as the primary endpoint, and change in serum Ca, ferritin, TSAT and bicarbonate as secondary endpoints; iPTH, serum iron, and TIBC were assessed as other variables. Subjects who met the eligibility criteria underwent a 1- to 2-week washout from phosphate binders. Subjects were randomized in a 1:1:1 ratio to 1, 6, or 8 g/day KRX-0502 as 1-g oral tablets TID for 4 weeks. A total of 146/154 randomized patients (94.8%) were included into ITT population for efficacy evaluation (50, 51 and 45 in the 1, 6, and 8 g/day groups, respectively); 122 of 154 patients randomised (79.2%) completed 4 weeks of study treatment. Treatment failure (serum Pi concentrations outside the allowable ranges) was the reason of discontinuation in 14 patients (9, 2, and 3 patients in the 1, 6, and 8 g/day groups, respectively), AE for 13 patients, withdrawal of consent for 1 patient, and investigator judgment for 1 patient.

The reduction in serum Pi was evident in the 6 and 8 g/day dose groups by Day 7 and remained relatively stable between Day 7 and the remainder of the 28-day treatment period. The mean reduction in serum Pi at the end of the treatment period was 0.10 mg/dL, 1.86 mg/dL, and 2.13 mg/dL in the 1, 6 and 8 g/day groups, respectively. The dose-response relationship was confirmed by regression analysis; at the end of treatment, the coefficient for dose in the ANCOVA regression model was statistically significant ($p<0.0001$).

With respect to iron-related efficacy variables, there was a small dose-dependent increase from baseline to the end of treatment in ferritin. The increases in the 6 and 8 g/day groups (90.1 and 90.2 ng/mL, respectively) were statistically significant compared to those in the 1 g/day group (−12.7 ng/mL). TSAT values decreased slightly from baseline to Day 28 in the 1 g/day group (−0.6%) and increased slightly in the 6 and 8 g/day groups (1.5% and 4.4%, respectively). Results of the ANCOVA and regression analyses were not significant. At Week 4, the mean observed serum iron values decreased slightly in the 1 g/day group (−1.9 µg/dL change from baseline) and increased in the 6 and 8 g/day groups (3.7 and 8.0 µg/dL, respectively). TIBC values decreased slightly, and to a similar extent, in all dose groups (−3.4, −3.8, and −4.3 µg/dL in the 1, 6, and 8 g/day groups, respectively).

Study GBA2-1 was a phase 2, 28 days, randomized, double-blind, placebo-controlled, parallel, comparative, dose-response study conducted in Japan to determine the effect and safety of JTT-751 at doses of 1.5, 3, and 6 g/day. Efficacy was assessed based on the change in serum Pi levels. The secondary efficacy assessments were the change in serum Ca (corrected) levels and change in Ca × Pi product, as well as the proportion of subjects who achieved a serum Pi level of 5.5 or 6.0 mg/dL. Additional assessments included iron and endocrine parameters. A total of 192 subjects received the investigational product. Of them, 39/49 (79.6%), 35/50 (70.0%), 20/45 (44.4%) and 35/48 (72.9%) of subjects in the 1.5, 3, 6 g/day and placebo groups, respectively, completed the study. The primary reason for discontinuation was the TSAT levels of 50% or more (25 subjects: 7, 8, 8 and 2 subjects in 1.5, 3, 6 g/day and placebo groups). 12 subjects discontinued due to the serum P level: 9 subjects in the 6 g/day group with <3 mg/dL and 3 subjects in the placebo group with ≥10 mg/dL. AEs were reason of discontinuation in 3 subjects: 2 subjects in the 3 g/day group and 1 subject in the placebo group.

After treatment (Week 4), changes in mean serum Pi of 0.00, −1.28, −2.16, and −4.10 mg/dL were observed for the Placebo, 1.5-, 3-, and 6-g/day treatment groups, respectively, and a decreased serum Pi level showed dose response up to 6 g/day. The proportion of subjects who achieved the serum Pi level of ≤ 6.0 and ≤ 5.5 mg/dL on the observation day of Week 4 was 96.3% and 92.6%, respectively, in the 6-g/day group. The serum Ca (corrected) levels increased significantly in the 6-g/day group compared with the placebo group, but this

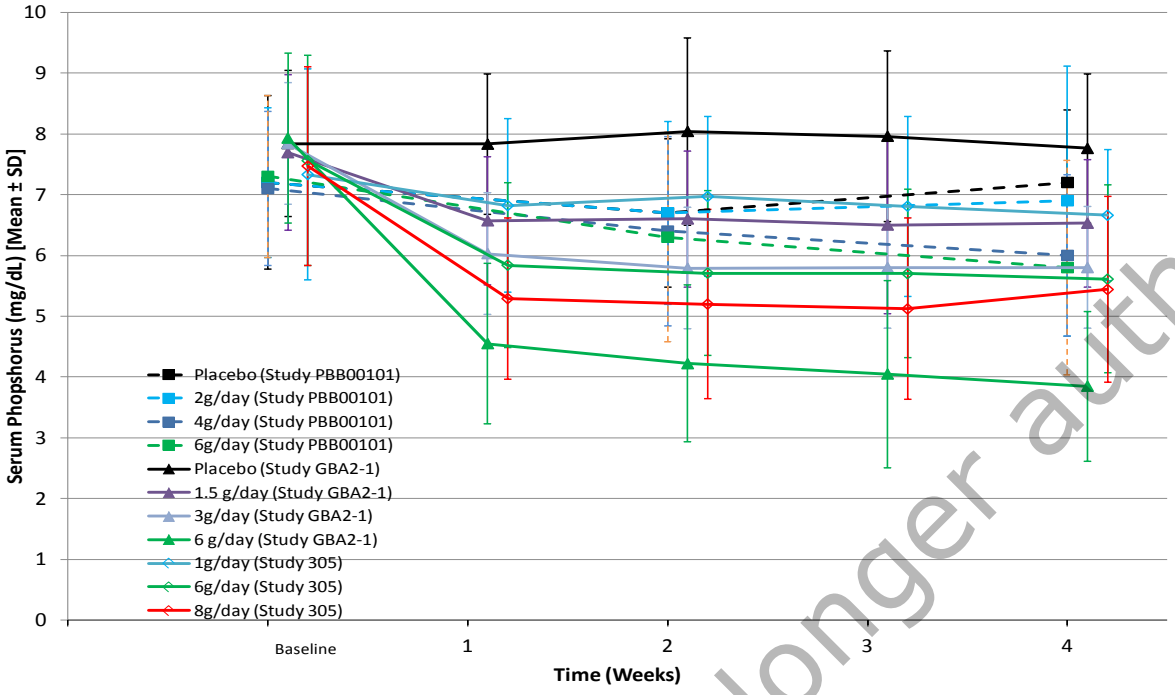
change was not clinically relevant. The administration of JTT-751 reduced the Ca × P product (corrected), and the dose response was observed. The change was considered to be mainly due to a reduction in serum Pi.

Study PBB00101 was a phase 2, 28 days, randomized, double-blind, placebo-controlled, dose-ranging study conducted in US/Taiwan to determine the effect of ferric citrate at doses of 2, 4, and 6 g/day. This study evaluated change from baseline to Day 14 and Day 28 in serum Pi concentration as the primary efficacy endpoint, Ca x Pi as secondary endpoint, and iron parameters and Ca concentration as other variables. Washout period for phosphate binder treatments lasted one- to two-week. Subjects who had a serum PO4 ≥ 5.5 mg/dL and ≤ 10 mg/dL by the end of washout were randomized in a ratio of 1:2:2:2 to 1 of 4 treatment groups: Placebo or 2, 4, or 6 g/day of ferric citrate. All subjects were to receive 4 capsules TID with meals, for 28 days. The ratio of active-to-placebo capsules for each subject was governed by the dose being administered. In total, 111/116 randomized and dosed patients (95.7%) were included into efficacy population; 14/16 patients (87.5%) completed placebo treatment, and 74/100 patients (74.0%) completed treatment with ferric citrate. The primary reasons for discontinuation were voluntary withdrawal (9/116; 7.8%), adverse events (8/116; 6.9%), and protocol violations (6/116; 5.2%). The mean serum Pi concentration increased during the washout period in all treatment groups. On Study Day 0, the mean Pi concentration was 7.2, 7.2, 7.1, and 7.3 mg/dL for the placebo, and 2, 4, and 6 g/day ferric citrate groups, respectively. After 14 days treatment, mean serum Pi decreased in all treatment groups compared with Day 0 (-0.5, -0.3, -0.8, and -1.2 mg/dL in the placebo and 2, 4, and 6 g/day ferric citrate groups, respectively), but the mean difference from placebo (0.2, -0.3, and -0.7 in the 2, 4, and 6 g/day groups, respectively) was not statistically significant.

After 28 days, mean serum Pi decreased in all treatment groups compared with Day 0 (-0,1, -0.3, -1.1, and -1.5 mg/dL in the placebo, and 2, 4, and 6 g/day ferric citrate groups, respectively). Serum Pi decreased in the 6 g/day group from 7.3 mg/dL on Day 0 to 5.8 mg/dL on Day 28, with a mean treatment difference of −1.5 mg/dL when compared with Placebo (p=0.0119); in other dose groups decrease was not statistically significant. When compared with Day 0, dose-dependent trends were also observed for increases in ferritin and TSAT after 28 days of treatment, however, without statistical significance. There were small increases in serum iron, ferritin, and TSAT values from baseline to Day 14. Between Day 14 and Week 4, there were no, or only slight, further increases in these parameters. At Week 4, the mean observed serum iron, ferritin, and TSAT values had shown the greatest change from baseline in the 6 g/day group (5.4 µg/dL, 41.9 ng/mL, and 1.9%, respectively). The greatest change from baseline for mean observed TIBC values was in the 2 g/day group (4.8 µg/dL).

Comparison of the results across dose-finding studies. The efficacy of KRX-0502 is dose proportional and occurs rapidly by week 1 (first point of measure). The lowering effect of KRX-0502 on phosphataemia is essentially stable for the rest of the duration of the studies. It was noted that KRX-0502 doses of 1 g/d and 2g/d were not different from placebo regarding lowering of phosphataemia. KRX-0502 doses of 6g/d and 8g/d in US CKD patients and of 3g/d in Japanese CKD patients lowered phosphataemia by ~ -1.5 to -2 mg/dl. The greatest effect on phosphataemia (-4.1 mg/dl) was seen with the dose of 6g/d in Japanese CKD patients.

Figure 2: Serum P levels over time following the administration of fixed dose of JTT-751/KRX-0502 in Studies PBB00101, GBA2-1 and 305 (mean ± SD)



Study PBB00101 included both US and Taiwanese CKD patients. While dose-response relationships were observed in both populations, serum P lowering effect was greater in the Taiwan population for identical doses (Table 4). This difference may be due to a lower dietary P intake (~800 mg/d vs. 900 mg/d) and a lower body-weight (60 kg vs. 90 kg) reported in the study. in two studies in CKD-ND patients where phosphaturia was monitored, the baseline phosphaturia was of 730 mg/d in the US (Study 204) and 430 mg/d in Japan (Study GBA4-4), i.e. 40% lower. Thus, it is possible that certain CKD patients may require lower doses of phosphate-binding agents to control serum P_i. Therefore, regular monitoring of serum P_i levels with titration to achieve target serum P_i goals is recommended, as described in the SmPC.

Table 4: Change in Serum Phosphorus From Baseline to End of Treatment Period by US and Taiwan Subjects

Time Point	Statistic	US			Taiwan		
		2 g/day (N=17)	4 g/day (N=20)	6 g/day (N=18)	2 g/day (N=16)	4 g/day (N=14)	6 g/day (N=15)
Baseline	Mean (mg/dL)	7.09	7.09	7.12	6.95	6.65	7.08
Day 28	Mean change[a] (mg/dL)	-0.89	-1.07	-1.09	-0.53	-1.32	-2.35

[a] *Mean change calculated from baseline (Day 0) to Day 28. Only subjects with both a pre- and post-baseline serum phosphorus assessment were included in this calculation.*

N=number in population that was randomized and received a dose of study treatment; US=United States.

2.5.2. Main studies

Two pivotal studies were conducted: study 304 and study 204. Both were multicenter, randomized studies. Study 304 was open-label phase 3 study in CKD 5D subjects, which consisted active-controlled period, followed

by placebo-controlled period. Study 204 was double blind, placebo controlled, 3-period phase 2 study in CKD ND subjects. Study 304 is continuing as long term (up to 48-week) open-label safety extension study 307 (ongoing).

Methods

- **Study participants**

Study 304

Main inclusion criteria at screening (visit 0): (1) adult subjects with CKD stage 5 on thrice-weekly HD or PD for ≥3 months prior to the Screening Visit; (2) taking ≥ 3 and ≤ 18 tablets/capsules per day of calcium acetate, calcium carbonate, lanthanum carbonate, and/or sevelamer, or any other agent serving as a phosphate binder, or any combination of these agents; (3) serum P_i ≥ 2.5 mg/dL and ≤ 8.0 mg/dL, serum ferritin <1000 ng/mL, and TSAT <50%; (4) Life expectancy >1 year. To be eligible for randomization, serum P_i had to be ≥ 6.0 mg/dL at the end of the Washout Period.

Exclusion criteria: (1) Serum P ≥10.0 mg/dL in all of the 3 months prior to the Screening Visit; (2) Previous intolerance to oral ferric citrate; (3) Intolerance to oral iron-containing products, calcium acetate and sevelamer carbonate; (4) Absolute requirement for oral iron therapy, for Vitamin C (multivitamins [Nephrocaps, Renaphro, etc.] allowed), for calcium-, magnesium-, or aluminum-containing drugs with meals; (5) various other conditions: Parathyroidectomy <6 months prior to Screening Visit ; symptomatic gastrointestinal bleeding or inflammatory bowel disease; history of multiple drug allergies/intolerances, malignancy in the last 5 years; planned surgery or hospitalization during the trial (except scheduled outpatient access surgery, eye laser surgery, etc).

Study 204

Inclusion criteria: (1) adult subjects (≥ 18 years) with CKD stage 3-5 with anaemia (Hgb >9.0 and <12.0 g/dL) and hyperphosphatemia who had failed a low phosphate diet, including subjects on and not on phosphate binders; (2) serum P_i: (a) Subjects on phosphate binder(s) at Screening with serum P_i ≥ 2.5 and ≤ 5.5 mg/dL at Screening (visit 0), and ≥ 4.0 and <6.0 mg/dL after a 2-week Washout Period after discontinuing phosphate binders; (b) De novo subjects who were not taking any phosphate binder with serum P_i ≥ 4.0 and <6.0 mg/dL at Screening ; (3) eGFR <60mL/min, iPTH ≤ 600 pg/mL, serum ferritin ≤ 300 ng/mL, and TSAT ≤ 30% at Screening; (4) Hb > 9.5 g/dL and < 12.0 g/dL at Screening, and Washout (if needed); (5) If on Vitamin D therapy, dose had to be stable.

To enter the 12-week Treatment Period, a subject's serum P had to be ≥4.0 and <6.0 mg/dL and hemoglobin (Hgb) had to be >9.0 and <12.0 g/dL at their qualifying visit (visit 1).

Exclusion criteria were similar to those in study 304. In addition, exclusion criteria included (1) acute kidney injury; kidney transplant or dialysis anticipated 16 weeks prior to Screening; (2) Cause of anaemia other than iron deficiency or chronic kidney disease; (3) History of haemochromatosis; (4) Absolute requirement for IV or oral iron therapy, ESA therapy, blood transfusion; (5) administration of IV iron, ESA, or blood transfusion 8, 4, and 8 weeks prior to screening, respectively; (6) Niacin or nicotinamide administered within 4 weeks prior to Screening (however, multivitamins were allowed). Exclusion criteria No 1 and 3 mentioned above for study 304, were not exclusion criteria for study 204.

- **Treatments**

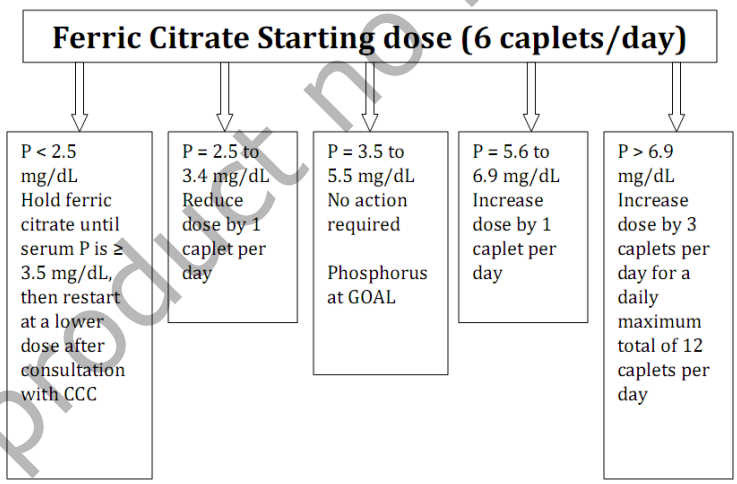
Study 304

The applicant provided a comparative to active control and to placebo study report in CKD 5D subjects, which included 3 consecutive periods: up to 2-week phosphate binder washout period; 52-week active-controlled safety assessment period (SP), and 4-week placebo-controlled efficacy assessment period (EAP). Study sites were located at 58 sites in the US and 2 sites Israel; 58 of these site enrolled subjects. A total of 441 subjects were randomised in Safety assessment period (SP), and 192 of them were re-randomised for EAP.

Study medication was taken TID with meals or 1 hour after meal. During SP, subjects were randomized in a 2:1 ratio to an initial dose of 6 g/day of KRX0502 (at 1 g caplets (tablets)) or active control consisting of calcium acetate (at 667 mg capsules) or sevelamer carbonate (at 800 mg tablets) or any combination of calcium acetate or sevelamer carbonate. Calcium acetate and sevelamer carbonate starting doses were chosen based on the last dose administered before Washout Period or at the discretion of the Principal Investigator (PI) if the phosphate binder regimen was altered. Titration of calcium acetate and/or sevelamer carbonate was to be according to the package inserts, and/or at the discretion of the PI. During SP, serum P and Ca was assessed at Visit 4 (Randomization Visit), Visit 5 (Week 1), Visit 6 (Week 2), and every two weeks from Visit 6 until Visit 11 (Week 12), then monthly, including the Final Visit (Visit 21, Week 52).

The KRX-0502 doses were titrated to a maximum daily dose of 12 g to achieve the target serum P_i of 3.5 to 5.5 mg/dL (see Figure 3). At the end of the SP, subjects in the KRX-0502 group were re-randomized to a 4-week EAP in a 1:1 ratio to continue treatment with KRX-0502 or switch to placebo.

Figure 3: KRX-0502 Titration Schedule in study 304, PS and EAP



Concomitant therapies: The use of vitamin D (or analogues) and cinacalcet was at the discretion of the Investigator. IV iron therapy was permitted in subjects whose ferritin was ≤ 1000 µg/L and the TSAT was ≤ 30%, with the dose at the discretion of the Investigator. Use of IV iron outside these parameters could occur with the approval of the study's PI. Erythropoietin use was permitted, with dose adjustments at the discretion of the Investigator or site. Ca supplements should be taken at bedtime or two hours or more prior to or after a patient's meal or snack; use of dialysate Ca was at the discretion of PI or treating physician.

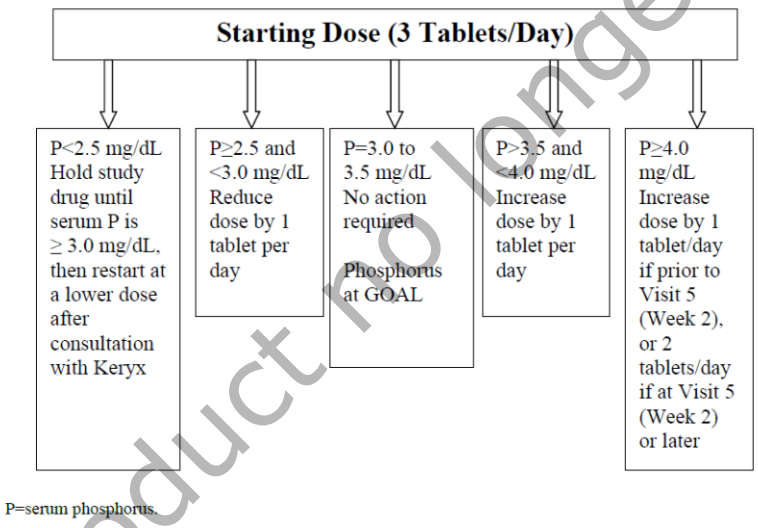
Prohibited therapies: Non-study phosphate binders were not allowed, as well as oral iron therapy, Ca-containing drugs taken within 2 hours of food ingestion, Vitamin C supplements (daily water-soluble vitamins that included

a small amount of vitamin C [eg, Centrum®, Nephrocaps®, and Renaphro®] ≥2 hours prior to or following food ingestion or at bedtime were allowed).

Study 204

The applicant provided a comparative to placebo study report in CKD ND subjects, which included 2 consecutive periods: up to 2-week phosphate binder washout period, followed by 12-week placebo-controlled period. Following the completion of the Washout Period subjects were randomized in a 1:1 ratio to receive either 3 g/day KRX-0502 or matching placebo; de novo subjects were randomized immediately. Study medication (KRX-0502 at 1 g tablets or matching placebo) was taken TID with meals. The starting dose of study medication was 3 g/day. The KRX-0502 doses were titrated to a maximum daily dose of 12 g to achieve the target serum P_i of 3.0 to 3.5 mg/dL by measuring firstly after 1 week and later every other week. (see Figure 4). If a subject had a serum P_i ≥6.0 mg/dL for 2 visits in a row (at least 7 days apart) during the 12-week Treatment Period after Visit 3 (Day 0), the subject was considered a treatment failure, stopped treatment with the study drug, and exited the study.

Figure 4: KRX-0502 Titration Schedule in study 204



Concomitant therapies: Changes in the prescribed dose or frequency of vitamin D were not permitted during this study. The maximum dose of cholecalciferol was 2000 IU every day beginning at Screening (Visit 0). Calcium supplements and daily water-soluble multivitamins were to be taken at bedtime or at least 2 hours or more prior to or after a subject's. Subjects were encouraged to maintain a stable dose and type of multivitamin (if any) throughout the study.

Prohibited therapies: Non-study phosphate binders, cinacalcet, niacin and nicotinamide, Vitamin C supplements were not allowed for the enrolled subjects. IV iron, ESAs, and blood transfusions were not permitted for a predefined period prior to Screening or at any time during the study. The use of oral iron was not permitted during the study. If a subject's Hgb was <9.0 g/dL for 2 visits in a row (at least 7 days apart) during the 12-week Treatment Period after Visit 3 (Day 0), the subject was considered a treatment failure, stopped treatment with the study drug, and exited the study.

- **Objectives**

In study 304, the primary efficacy objective was to determine the efficacy of KRX-0502 as a treatment for hyperphosphatemia in a 4-week EAP in subjects with ESRD who were undergoing either HD or PD. The alternative primary efficacy objective was to determine the non-inferiority of KRX-0502 as a treatment for hyperphosphatemia at Week 12 vs. sevelamer carbonate in SP. The main safety objective was to determine the long-term safety over 52 weeks of up to 12 caplets/day of KRX-0502

In study 204, objectives were to compare the efficacy and safety of KRX-0502 to placebo in managing serum P and iron deficiency anaemia in subjects with Stage 3 to 5 CKD ND as measured by changes in TSAT and serum P over a 12-week Treatment Period.

- **Outcomes/endpoints**

Study 304

The primary efficacy endpoint was the change in serum P_i during 4 weeks withdrawal period C (from Week-52-baseline to the end of EAP (Week 56)). An additional alternative primary efficacy endpoint was to determine the difference in serum P between KRX and sevelamer (non-inferiority vs. sevelamer carbonate) in terms of change in serum P_i from baseline to Week 12. Secondary endpoints: (1) change in serum ferritin and TSAT from Baseline to Week 52; (2) cumulative IV iron and ESA administration use compared to the active control from randomization to Week 52. Exploratory efficacy variables included: (1) % of subjects achieving serum $P_i \leq 5.5$ mg/dL at defined time-points during the study (at W12, 24, 36, 48 and 52 and (2) at week 56 (during EAP); (3) % of subjects achieving serum $P_i \geq 9.0$ mg/dL; (4) change in serum Ca; serum iron; TIBC; Ca × P product; iPTH; 25-dihydroxy-vitamin D3, vitamin A, vitamin B-12, vitamin E, vitamin K and folic acid; serum bicarbonate; lowdensity lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides during the study.

Study 204

Co-primary efficacy endpoints were the changes in TSAT and serum P from baseline (Visit 3) to the end of the 12-week Treatment Period (Visit 10 [Week 12]). Secondary endpoints included the change from baseline in Ferritin, Hgb, Intact FGF-23, Urinary phosphorus, and eGFR at Week 12. The supportive and exploratory endpoints at Week 12 for this study included change from baseline in serum Ca × P Product, serum and urinary Ca, serum carbon dioxide/bicarbonate levels, UIBC, TIBC, serum iron, HCT, iPTH, C-terminal FGF-23.

- **Sample size**

Study 304: Approximately 350 subjects were to be randomized at a 2:1 ratio to either KRX-0502 (~230 subjects) or active control (~120 subjects). It was assumed that up to 30% of the subjects in the KRX-0502 group would discontinue from the study before entering the EAP, so 140 to 160 subjects in the KRX-0502 group were planned to be re-randomized at a 1:1 ratio to receive either KRX-0502 (approximately 70 to 80 subjects) or placebo (approximately 70 to 80 subjects). This sample size was considered to provide at least 90% power to detect a treatment difference, assuming that the treatment difference was ≥1.2 mg/dL and the common SD was 2. This assumption was based on the results from a previous Phase 2 Study PBB00101, where the mean difference from baseline to endpoint (week 4) in serum P for the 6 g/day dose vs. placebo was ~ -1.5 mg/dL and the SD was ~2.0. The SD was also similar among the other treatment groups. Under these assumptions (slope from 1 g to 6 g=1.4/5=0.28, between the 6 g/day and 1 g/day groups) and with the inclusion of an even higher dose group (8 g/day), a sample size of 150 subjects (50 subjects/group) would also provide over 90% power to detect a positive slope, assuming a continued positive effect for the 8 g/day dose.

Study 204: 149 subjects were randomized in a 1:1 ratio to receive study drug (75 and 74subjects to KRX-0502 and to placebo, respectively). It was anticipated that the dropout rate during the 12-week Treatment Period would be approximately 20%, with ~110 subjects completing 12 weeks of treatment (~55 subjects in each treatment group). It was anticipated that the baseline TSAT levels at Day 0 would be ~20% in both treatment groups, and TSAT levels at Week 12 would be ~30% in the KRX-0502 group and 20% in the placebo group. It was also anticipated that the common SD would be ~5%. Based on these parameters, the study was expected to have at least 80% power to detect the hypothesized difference of 10% between the 2 groups (alpha=0.05, 2 sided). It was anticipated that the baseline serum P at Day 0 would be ~4.5 mg/dL in both treatment groups, and the ending serum P at Week 12 would be ~4.2 mg/dL in the KRX-0502 group and 4.5 mg/dL in the placebo group. The common SD was ~0.5 mg/dL. Based on these parameters, the study should have at least 80% power to detect the hypothesized *difference of 0.3 mg/dL* between the 2 groups (alpha=0.05, 2 sided).

- **Randomisation**

In **study 304**, there were 2 consecutive randomisations: (1) Subjects who completed the Washout Period were randomized in a 2:1 ratio to the KRX-0502 group or the active-control group of calcium acetate or sevelamer carbonate or any combination of both at the discretion of the PI. Dosing was initiated at Visit 4 (Day 0) following the completion of baseline laboratory assessments; (2) Subjects entering the 4-week EAP on KRX-0502 were re-randomized in a 1:1 ratio to continue treatment with either KRX-0502 or placebo at the Final Visit for Safety (Week 52). In order to randomize subjects, sites used IWRS managed by Bilcare Research Inc.

In **study 204**, subjects were randomized in a 1:1 ratio to the KRX-0502 group or matching placebo group. Randomization occurred on or before Visit 3 (Randomization) following completion of a 2-week Washout Period for subjects who were on a phosphate binder at Screening, or immediately following the Screening and Randomization Periods for subjects not taking a phosphate binder. Randomization was conducted by IWRS managed by Sharp Clinical Services using a randomization list.

- **Blinding (masking)**

There was certain blinding employed in main studies. The applicant noted that given the physiologic effects of ferric citrate administration (dark stools), formal blinding was not used in the Phase 3 programme for KRX-0502. However, in the 4-week placebo-controlled period of Study 304 and in the 12-week placebo controlled Study 204, subjects were blinded to study treatment through the use of a matching placebo. Primary efficacy endpoint and most of the secondary efficacy endpoints were based on objective laboratory measurements conducted by central laboratory staff blinded to treatment and dose, therefore the open-label design was not considered to have the potential to bias the efficacy results of the studies by the applicant.

- **Statistical methods**

Study 304: The Full Analysis (FA) Population consisted of all subjects who took at least 1 dose of study medication and had a baseline and at least 1 post-baseline serum P value. The Safety Population consisted of all subjects who took at least 1 dose of study medication. Unless otherwise stated, all analyses were performed using SAS® Version 9.2 or higher, and all hypothesis tests were conducted at a two-sided significance level of 0.05. P-values were presented with 3 decimals and p-values that were less than 0.001 were presented as <0.001. If the rounded result was a value of 1.000, it was displayed as >0.999. The continuous data were summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median,

25th and 75th percentiles, minimum, and maximum. Frequencies and percentages were used to summarize categorical (discrete) data. Unless otherwise stated, confidence intervals, when presented, were constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals were constructed using the normal approximation without continuity correction.

The efficacy and safety analyses were based on Full Analysis population that consists of all patients who take at least one dose of study medication and provide baseline and at least one post-baseline efficacy assessments. Supportive sensitivity analyses were performed for the primary efficacy endpoint, and the secondary efficacy endpoints noted above, by longitudinal data analysis. These analyses were based on MMRM methods. All follow-up observations during the efficacy assessment period were utilized; missing values remained as missing, i.e. no attempt was made to impute missing values, and only observed values were used in the data analysis. The model included terms for treatment group, baseline value, weeks post baseline, treatment by weeks post baseline interaction. Treatment differences between ferric citrate and all active control binders as well as the differences between ferric citrate and sevelamer carbonate as a single agent at Week 12 in terms of change from Visit-4 baseline in serum phosphorus, phosphorus times calcium product, and in serum calcium were analyzed. These variables were analyzed using LOCF methodology. ANCOVA was employed. The model included treatment (fixed effect), and Visit-4 baseline (covariate). The least square mean estimates of the treatment effects as well as the 2-sided 95% confidence intervals of the treatment effects were derived. Non-inferiority was claimed if the lower-bound of the two-sided 95% confidence interval of the treatment difference is within 20% of least square mean of the control. Missing efficacy data were imputed using LOCF method for the primary analysis on the primary efficacy variable. The MMRM methods were used as a sensitivity analysis to the primary efficacy variable. Unless stated otherwise, all the secondary and supportive endpoints with multiple observations were analyzed using LOCF methodology

The primary efficacy endpoint of trial is defined as the change in serum phosphorus from baseline (Visit 21, Week 52) to end of the four-week efficacy period (Visit 25, Week 56) versus placebo in the Full Analysis population. The primary efficacy variable was analyzed using an ANCOVA model with treatment as the fixed effect and Week-52 baseline as the covariate. Between-treatment differences were estimated and two-sided 95% confidence intervals for the differences were presented. Missing efficacy data were imputed using LOCF method for this primary analysis on the primary efficacy endpoint only. The *secondary endpoints* for this trial included change from baseline in ferritin at week 52, change from baseline in TSAT at week 52, cumulative use of IV iron over 52 weeks, and cumulative use of EPO (ESA) over 52 weeks.

When multiplicity is present, the usual frequentist approach to the analysis of clinical trial data may necessitate an adjustment to the type I error. In order to control overall Type I error rate at 5%, this study applied gatekeeping sequential strategy with following ranking: 1) Primary endpoint: change in serum phosphorus from baseline (Visit 21, Week 52) to end of the four-week efficacy period, 2) Secondary endpoint: Change from baseline in ferritin at Week 52, 3) Secondary endpoint: Change from baseline in TSAT at Week 52, 4) Secondary endpoint: Cumulative use of IV iron over 52 weeks, 5) Secondary endpoint: Cumulative use of EPO (ESA) over 52 weeks. Each of these five comparisons was made at a type I error rate of 5%. A comparison was claimed as significant for this study only if all previous comparisons, if any, were significant. There was no adjustment for multiplicity needed for these supportive and exploratory endpoints.

Safety analyses were performed for the safety population. Safety evaluations were based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the patient's physical examination, vital signs, and clinical laboratory results. Safety variables were tabulated and presented by study period separately. Summary tables of vital signs and change from appropriate baseline were presented for all scheduled visits where vital signs were assessed.

Study 204: Intended-to-treat (ITT) population consisted of all subjects who were randomized in the study, had a baseline laboratory value, had taken at least 1 dose of study drug, and had at least 1 post-baseline laboratory value. The Safety Population consisted of all subjects who took at least 1 dose of study medication. The efficacy analyses were based on the ITT population. The primary efficacy endpoints of this trial were the effect of KRX-0502 (ferric citrate) vs. placebo with respect to the change in TSAT and serum phosphorus levels from baseline (Visit 3) to end of the 12-week Treatment Period (Visit 10). The primary efficacy variables were analyzed using an ANCOVA model with treatment as a fixed effect and baseline value of the endpoint being analyzed as the covariate.

The comparisons were tested in the following order at a 5% significance level:

1. The change from baseline in TSAT at week 12; and

2. The change from baseline in serum phosphorus at week 12.

To control overall Type I error rate at 5%, a comparison was significant only if all previous comparisons, if any, were significant.

In those cases where a subject withdraws prematurely, including treatment failures, the subject's most recent value was considered to have remained unchanged through the end of the 12-week Treatment Period. Distributional assumptions underlying the ANCOVA model were assessed. The assumption of normality was assessed by examination of the normal probability plot. If assumptions appeared to be grossly violated, alternative analyses (e.g., non-parametric method Wilcoxon rank-sum test) would be performed. Missing efficacy data were imputed using the last observation carried forward (LOCF) method for the primary analyses on the primary efficacy variables.

The secondary endpoints for this trial included: The change from baseline in ferritin, in hemoglobin, in intact fibroblast growth factor 23 (FGF23), in urinary phosphorus, baseline in estimated glomerular flow rate (eGFR) at week 12; The above variables were analyzed with ANCOVA using LOCF methodology and baseline as the covariate. Supportive sensitivity analyses were performed for the primary efficacy endpoint, and the secondary efficacy endpoints, by longitudinal data analysis with maximum likelihood estimation and unstructured modeling of time and the within-subject error correlation structure. These analyses were based on Mixed Model Repeated Measures (MMRM) methods (Verbeke, 2002; Mallinckrodt, 2003). All follow-up observations were utilized; missing values were remained as missing, i.e. no attempt was made to impute missing values, and only observed values were used in the data analysis. The model included terms for treatment group, baseline value, weeks post baseline, treatment by weeks post baseline interaction. The MMRM was implemented.

The following exploratory efficacy endpoints were also considered for descriptive purposes only, with no adjustment for multiplicity: the change from baseline in some variables (serum calcium x phosphorus product, serum calcium, urinary calcium, serum carbon dioxide/bicarbonate levels, unsaturated iron binding capacity (UIBC), iron binding capacity (TIBC), serum iron, hematocrit, intact parathyroid hormone (iPTH), C-terminal fibroblast growth factor 23 (FGF23) at week 12.

The above variables were analyzed using LOCF methodology. ANCOVA was employed. The model included treatment (fixed effect), and baseline (covariate). No interim analysis was performed. To control overall Type I error rate at 5%, gatekeeping sequential strategy was applied. The ranking of the primary endpoints and the secondary endpoints were as follows: (1) change from baseline in TSAT at week 12;(2) change from baseline in serum phosphorus at week 12;(3) change from baseline in ferritin at week 12;(4) change from baseline in hemoglobin at week 12;(5) change from baseline in intact fibroblast growth factor 23 (FGF23) at week 12;(6) change from baseline in urinary phosphorus at week 12; and (7)change from baseline in estimated glomerular

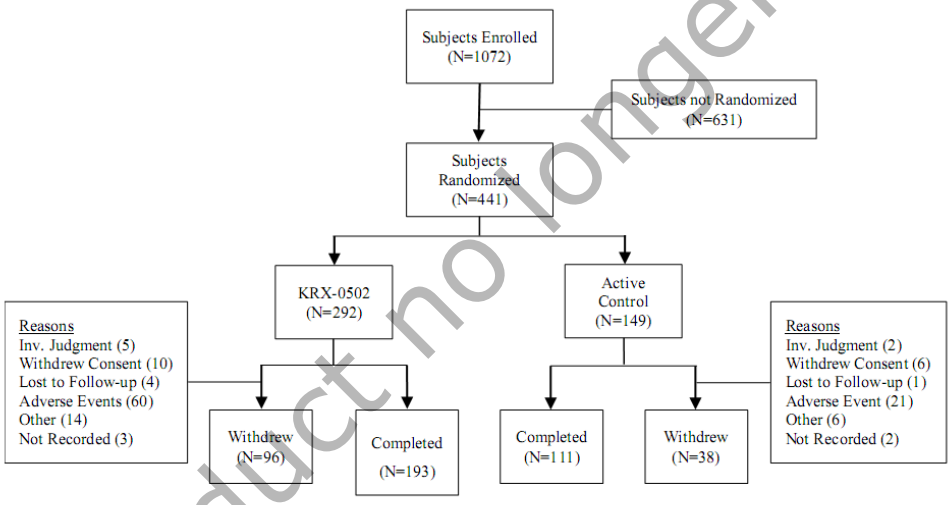
flow rate (eGFR) at week 12. Each of these six comparisons were made at a type I error rate of 5%. A comparison would be claimed as significant for this study only if all previous comparisons, if any, were significant.

Results

- **Participant flow**

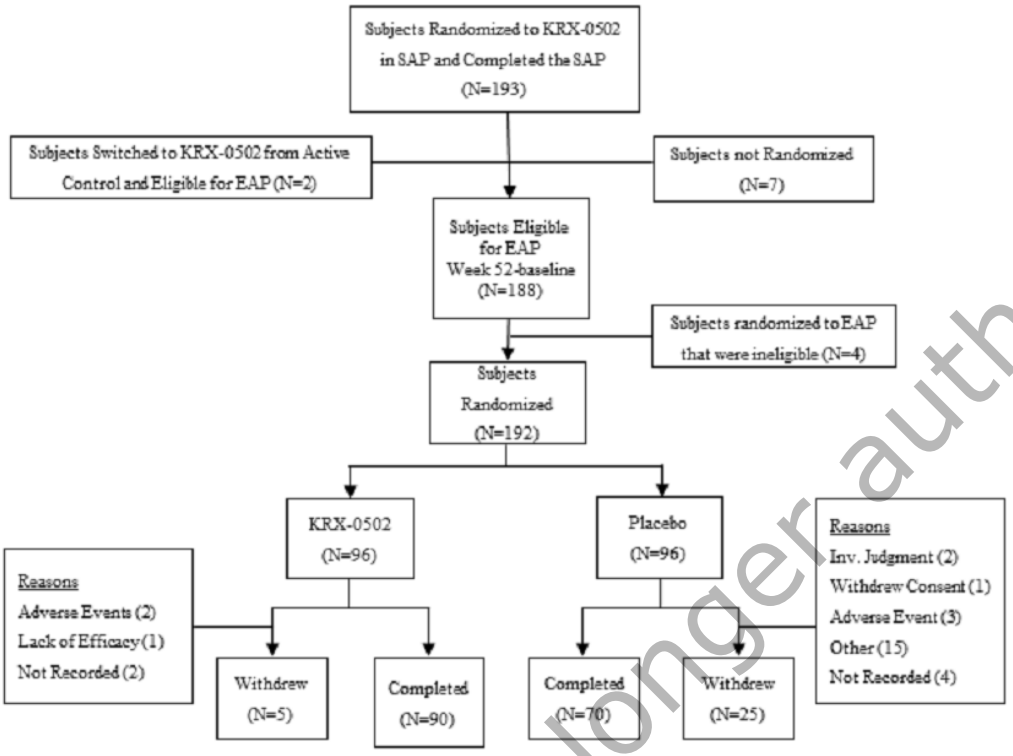
Study 304. Subject disposition and reasons for withdrawal during SP and EAP are provided in Figure 5 and Figure 6, respectively. During SP, withdrawal rates were higher in the KRX-0502 group (96/292 subjects, 32.9%) vs. active control group (38/149 subjects, 25.5%); 3 randomised subjects did not receive study treatment. During EAP, withdrawal rates were lower in the KRX-0502 (5/96, 5.2%) group vs. placebo group (25/96, 26.0%).

Figure 5. Subject disposition and reasons for withdrawal in SP of study 304.



Sources: Table 14.1.1.1 and Ad Hoc Table 1.
Note: Four subjects (Subject 109-008, Subject 122-009, Subject 129-039, and Subject 144-002) originally randomized to active control during the Safety Assessment Period were switched to KRX-0502 due to hypercalcemia.
Inv.=Investigator; KRX-0502=ferric citrate; N=number of subjects.

Figure 6. Subject disposition and reasons for withdrawal in EAP of study 304.



Sources: Table 14.1.1.1 and Appendix 16.1.7, Ad Hoc Listing 3 and Appendix 16.1.7, Ad Hoc Listing 8.
Note: Four subjects (Subject 109-008, Subject 122-009, Subject 129-039, and Subject 144-002) originally randomized to active control during the SAP were switched to KRX-0502 due to hypercalcemia. Two of these subjects (Subject 109-008 and Subject 129-039) completed the SAP and were eligible for randomization to the EAP. The other 2 subjects (Subject 122-009 and Subject 144-002) did not complete the SAP and were ineligible to be randomized to the EAP but were randomized.
EAP=Efficacy Assessment Period; Inv.=Investigator; KRX-0502=ferric citrate; N=number of subjects; SAP=Safety Assessment Period

Study 204: Subject disposition and reasons for withdrawal are provided in Table 5. In total, 111/149 subjects (74.5%) completed the study. More subjects in the KRX-0502 group (81.3%) completed the study than in the placebo group (67.7%). Overall, 12 subjects terminated early due to treatment failure, 1 subject (1.3%) in the KRX-0502 group (due to hemoglobin <9.0 g/dL for 2 consecutive study visits) and 11 subject (14.9%) in the placebo group (9 due to hemoglobin <9.0 g/dL and 2 due to serum phosphorus ≥6.0 mg/dL for 2 consecutive study visits). More subjects in the KRX-0502 group (8.0%) withdrew from the study due to an AE than in the placebo group (4.1%).

One placebo subject (Subject 512-006) was randomized but never received a dose of study drug and was therefore excluded from the safety population. Three subjects randomized to receive KRX-0502 (Subjects 502-038, 504-002, and 510-010) and 5 subjects randomized to receive placebo (Subjects 502-041, 505-021, 512-006, 521-032, and 524-006) were excluded from the ITT population since they did not meet the criteria for inclusion into the ITT population.

Table 5: Summary of Subject Disposition in study 204

Disposition	KRX-0502 (N=75)	Placebo (N=74)	Overall (N=149)
Number of screened subjects, n			399
Number of enrolled subjects, n			149
Number of randomized subjects, n (%)	75 (100.0%)	74 (100.0%)	149 (100.0%)
Number of subjects in Safety population, n (%)	75 (100.0%)	73 (98.6%)	148 (99.3%)
Number of subjects in ITT population, n (%)	72 (96.0%)	69 (93.2%)	141 (94.6%)
Number of subjects who completed the study, n (%)	61 (81.3%)	50 (67.6%)	111 (74.5%)
Number of subjects who terminated early, n (%)	14 (18.7%)	24 (32.4%)	38 (25.5%)
Reason for early termination, n (%)			
Treatment failure	1 (1.3%)	11 (14.9%)	12 (8.1%)
Hemoglobin <9.0 g/dL[a]	1 (1.3%)	9 (12.2%)	10 (6.7%)
Phosphorus ≥6.0 mg/dL[a]	0	2 (2.7%)	2 (1.3%)
Withdrew consent	6 (8.0%)	5 (6.8%)	11 (7.4%)
Lost to follow-up	0	1 (1.4%)	1 (0.7%)
AE[b]	6 (8.0%)	3 (4.1%)	9 (6.0%)
Other	1 (1.3%)	4 (5.4%)	5 (3.4%)

[a] *Treatments failures are defined as having serum phosphorus ≥6.0 mg/dL or hemoglobin <9.0 g/dL for 2 consecutive study visits.*

[b] *AE was listed as the primary reason for discontinuation.*

AE=adverse event; ITT=Intent-to-Treat; N=number in the population and treatment group (denominator for percentages, where applicable); n=number of observations (numerator for percentages, where applicable).

- **Recruitment**

Study 304 recruitment was initiated in December 2010 and completed in November 2012.

Study 204 recruitment was initiated in November 2012, and completed in October 2013.

- **Conduct of the study**

In **Study 304**, there were 784 protocol deviations reported, including 196 non-significant deviations/observations related to the administration of IV iron. There were 18 protocol deviations in 12 subjects that involved enrolment criteria (10/18 events) and/or prohibited medication (8/18 events). During the study period, one protocol amendment was made. Three main changes were introduced: (1) the number of patient to be randomized was increased from 300 to~350; (2) the frequency of monitoring of iron parameters was increased from every 12 weeks to every 4 weeks; (3) if a patient in the active control group developed

hypercalcemia on either calcium acetate as a single agent or in the combination of calcium acetate and sevelamer carbonate, these patients were eligible to be switch to treatment with KRX.

In study **204**, 41 non-laboratory related protocol deviations occurred in 26 subjects during the study, the majority (87.8%) of them at screening (39.0%) or due to the study drug dose not being titrated according to the protocol (46.3%). Numerous laboratory-related protocol deviations were provided as by-patient list only. In addition, severity of deviations was not provided. During study period, 2 protocol amendments were made during study period. In the first, inclusion criteria for TSAT at Screening were changed from ≤20% to ≤30%. In the second, the following main changes were introduced: (1) Increased number of study sites (from ~ 10-15 to ~25), subjects to screen in one site (from ~35 to ~40), prolonged time period allocated for subject enrolment (from ~3 to 6 months to ~6 to 9 months); (2) Change in drug administration schedule; (3) Change in inclusion criterion for hemoglobin (from ≥9.5 and <11.5 g/dL at Screening and Washout to >9.0 and <12.0 g/dL); (4) ferritin was considered as a secondary efficacy endpoint instead of primary.

- **Baseline data**

Study 304

The majority of subjects randomized into the study were Black (range: 52.7% to 54.4%) and men (range: 57.5% to 62.3%). In EAP, there was a larger proportion of Black and male subjects randomized to KRX-0502 (64.8% and 73.6%, respectively) than to placebo (52.7% and 48.4%, respectively). The mean age was ~54 years across periods and treatment groups. The mean weight at baseline was ~90 kg. The Applicant claims that study population in Study 304 was generally well balanced with respect to subject demographics across the 2 treatment groups at baseline (Table 6). The most common causes of CKD were diabetes (range 40.9% to 44.5%) and hypertension (range 39.9% to 43.8%). The majority of subjects were on HD; 3.9% and 2.1% of subjects in the KRX-0502 and active control groups, respectively, were on PD in the SP; 3.3% and 5.5%, respectively, were on PD in the EAP. A summary of prior and concomitant medications was not created for this study; the data is provided as a by-subject listing only.

Table 6. Summary of Demographics and Baseline Characteristics, FAP in study 304

Parameter	KRX-0502 Safety Assessment Period (N=281)	Active Control in Safety Assessment Period (N=146)	KRX-0502 in Efficacy Assessment Period (N=91)	Placebo in Efficacy Assessment Period (N=91)	Overall (N=427)
Age (year)					
Mean (SD)	54.5 (13.24)	53.7 (13.10)	54.7 (11.72)	54.2 (12.08)	54.2 (13.18)
(Min, Max)	(19, 90)	(19, 86)	(30, 86)	(21, 83)	(19, 90)
Age group, N (%)					
<65 years	223 (79.4%)	118 (80.8%)	73 (80.2%)	77 (84.6%)	341 (79.9%)
≥65 years	58 (20.6%)	28 (19.2%)	18 (19.8%)	14 (15.4%)	86 (20.1%)
Sex, N (%)					
Female	106 (37.7%)	62 (42.5%)	24 (26.4%)	47 (51.6%)	168 (39.3%)
Male	175 (62.3%)	84 (57.5%)	67 (73.6%)	44 (48.4%)	259 (60.7%)
Race, N (%)					
Asian	0	1 (0.7%)	0	0	1 (0.2%)
Black or African American	153 (54.4%)	77 (52.7%)	59 (64.8%)	48 (52.7%)	230 (53.9%)
White/Caucasian	114 (40.6%)	61 (41.8%)	28 (30.8%)	39 (42.9%)	175 (41.0%)
American Indian or Alaska Native	2 (0.7%)	1 (0.7%)	0	1 (1.1%)	3 (0.7%)
Native Hawaiian or Pacific Islander	0	2 (1.4%)	0	0	2 (0.5%)
Unknown	1 (0.4%)	0	0	1 (1.1%)	1 (0.2%)
Other	11 (3.9%)	4 (2.7%)	4 (4.4%)	2 (2.2%)	15 (3.5%)
Ethnicity, N (%)					
Hispanic or Latino	41 (14.6%)	23 (15.8%)	9 (9.9%)	14 (15.4%)	64 (15.0%)
Not Hispanic or Latino	239 (85.1%)	123 (84.2%)	82 (90.1%)	77 (84.6%)	362 (84.8%)
Weight (kg)[a]					
N	278	145	89	91	423
Mean (SD)	93.56 (27.542)	89.82 (24.160)	90.82 (25.190)	97.20 (28.414)	92.28 (26.463)
(Min, Max)	(44.2, 184.8)	(45.2, 175.8)	(47.3, 184.8)	(44.2, 182.3)	(44.2, 184.8)
Mean serum phosphorus (mg/dL)	**Study-baseline**		**Week-52-baseline**		
Mean (SD)	7.41 (1.630)	7.56 (1.744)	5.12 (1.189)	5.44 (1.459)	NA
(Min, Max)	(2.7, 15.0)	(4.3, 12.9)	(2.7, 8.5)	(1.1, 10.7)	NA

Sources: Table 14.1.2.2, Table 14.2.1.1, and Table 14.2.4.1.
[a] The numbers of subjects for weight were slightly smaller than indicated in the column headings, so it was specified.
KRX-0502=ferric citrate; Max=maximum; Min=minimum; N=number of subjects; NA=not applicable; SD=standard deviation.

During the SP of Study 304, exposure data are available for 281 subjects in the KRX-0502 group and 146 subjects in the active control group. The total mean duration of exposure was slightly longer on active control than on KRX-0502 (45.9 vs. 43.3 weeks); median exposure was 52 weeks in both treatment arms. Subjects on KRX-0502 initiated study drug at a dose of 6 g/day; the mean prescribed dose increased to 8.00 g/day by Week 12 and 8.78 g/day by the end of the SP (Week 52), ranging from 0 to 12 g/day. In the active control group, the mean prescribed dose increased from 7.71 to 8.71 pills/tablets per day from Study-baseline to Week 12 and remained at ~9 pills or tablets per day for the remainder of SP. In subjects receiving active control as single agents (n=117), the mean prescribed daily dose of sevelamer (n=78) increased from 7.67 pills per day at baseline to 9.57 pill per day at Week 52; the mean daily dose of calcium acetate (n=39) remained relatively constant at approximately 7.25 pills per day. The cumulative mean (SD) daily prescribed dose of KRX-0502 over the 52-week treatment period in Study 304 were 8.1 (2.4) g/day (corresponding to 8.1 tablets/day). For sevelamer (n=78) and calcium acetate (n=39), the mean (SD) number of tablets prescribed per day was 8.7 (2.8) and 7.6 (2.8), respectively.

Study 204

The majority of subjects were White/Caucasian (77.7%), female (64.9%), aged 65 years or older (56.1%) and had Stage IV CKD (52.7%) (Table 7). The mean baseline (SD) TSAT and serum P_i were similar in the KRX-0502 and placebo groups: TSAT 21.6% (7.44%) and 21.0% (8.26%), respectively, and serum P_i 4.5 (0.61) mg/dL and 4.7 (0.60) mg/dL, respectively.

Table 7: Summary of Demographic Characteristics in study 204 (Safety Population)

Demographic Characteristic	KRX-0502 (N=75)	Placebo (N=73)	Overall (N=148)
Age (year)			
n	75	73	148
Mean (SD)	65.8 (12.15)	64.5 (13.55)	65.1 (12.83)
Median	66.6	65.9	66.4
(Min, Max)	(25.4, 87.0)	(21.5, 88.1)	(21.5, 88.1)
Age group, n (%)			
<65 years	31 (41.3%)	34 (46.6%)	65 (43.9%)
≥65 years	44 (58.7%)	39 (53.4%)	83 (56.1%)
Sex, n (%)			
Female	51 (68.0%)	45 (61.6%)	96 (64.9%)
Male	24 (32.0%)	28 (38.4%)	52 (35.1%)
Race, n (%)			
Asian	0	1 (1.4%)	1 (0.7%)
Black or African American	16 (21.3%)	16 (21.9%)	32 (21.6%)
White/Caucasian	59 (78.7%)	56 (76.7%)	115 (77.7%)
Ethnicity, n (%)			
Hispanic or Latino	15 (20.0%)	21 (28.8%)	36 (24.3%)
Not Hispanic or Latino	60 (80.0%)	52 (71.2%)	112 (75.7%)
CKD stage at baseline, n (%)			
Other/missing	1 (1.3%)	1 (1.4%)	2 (1.4%)
Stage III	14 (18.7%)	16 (21.9%)	30 (20.3%)
Stage IV	39 (52.0%)	39 (53.4%)	78 (52.7%)
Stage V	21 (28.0%)	17 (23.3%)	38 (25.7%)

Source: Table 14.1.2.1
Note: Percentages are based on the total number of subjects who participated in each treatment group.

CKD=chronic kidney disease; max=maximum; min=minimum; N=number in the population and treatment group (denominator for percentages, where applicable); n=number of observations (numerator for percentages, where applicable);

- **Numbers analysed**

Study 304: Full Analysis (FA: all subjects who took > 1 dose of study medication and had a baseline and at least 1 post-baseline sP value) population was used for analyses of all primary and secondary efficacy endpoints. Safety analyses were conducted with safety population (SP, all subjects who took > 1 dose of study medication) and efficacy over placebo (for primary endpoint) was analysed in efficacy analysis set (EAS). Numbers of subjects in these populations are provided in Table 8.

Table 8. Numbers of subjects in study 304

Parameter	Statistics[1]	KRX-0502 in Safety Assessment Period (N=292)	Control in Safety Assessment Period (N=149)	KRX-0502 in Efficacy Assessment Period (N=96)	Placebo in Efficacy Assessment Period (N=96)	Overall (N=441)
Subjects Randomized	n (%)					441 (100.0%)
Subjects in the Safety Population						
No	n (%)	3 (1.0%)	0	1 (1.0%)	1 (1.0%)	3 (0.7%)
Yes	n (%)	289 (99.0%)	149 (100.0%)	95 (99.0%)	95 (99.0%)	438 (99.3%)
Subjects in the Full Analysis Population						
No	n (%)	11 (3.8%)	3 (2.0%)	5 (5.2%)	5 (5.2%)	14 (3.2%)
Yes	n (%)	281 (96.2%)	146 (98.0%)	91 (94.8%)	91 (94.8%)	427 (96.8%)
Subjects Randomized to Open-Label, Active Control Safety Assessment Period						
No	n (%)	0	0	0	0	0
Yes	n (%)	292 (100.0%)	149 (100.0%)	96 (100.0%)	96 (100.0%)	441 (100.0%)
Subjects Randomized to Open-Label, Placebo Control Efficacy Assessment Period						
No	n (%)	104 (35.6%)	145 (97.3%)	0	0	249 (56.5%)
Yes	n (%)	188 (64.4%)	4 (2.7%)	96 (100.0%)	96 (100.0%)	192 (43.5%)
Final Subject Status						
Subject Completed Safety Assessment Period[2]	n (%)	193 (66.1%)	111 (74.5%)	93 (96.9%)	95 (99.0%)	304 (68.9%)
Subject Completed Efficacy Assessment Period[2]	n (%)	156 (53.4%)	4 (2.7%)	90 (93.8%)	70 (72.9%)	160 (36.3%)
Subject Withdrawn	n (%)	96 (32.9%)	38 (25.5%)	5 (5.2%)	25 (26.0%)	164 (37.2%)

Note: [1]. Percentages are based on the total number of subjects enrolled in each treatment group.
Note: [2]. Completion is defined as completing the treatment period or study on study drug, and is derived from a combination of the Disposition and Adverse Events pages.

Study 204: ITT population was used for analyses of all primary and secondary efficacy endpoint and was defined as for Study 304 (all subjects who took > 1 dose of study medication and had a baseline and at least 1 post-baseline sP value). Safety analyses were conducted with safety population tht was defined as in Study 304. Numbers of subjects in these populations are provided in Table 8 above.

- **Outcomes and estimation**

Study 304

Primary efficacy endpoint

Administration of KRX-0502 maintained serum P_i from Week 52 to Week 56 (mean change of –0.24 mg/dL in ANCOVA model using LOCF, and -0.23 mg/dL in MMRM model) whereas the serum P_i increased in the Placebo

group (mean change of 1.79 mg/dL 95% CI [1.57, 2.15] in ANCOVA model using LOCF, and 1.46 mg/dL, 95% CI [1.49, 2.11] in MMRM model) in FA population. Serum P_i was significantly lower in the KRX-0502 group vs. Placebo group at Week 56 (ANCOVA model using LOCF: LS Mean = −2.18 mg/dL; p<0.0001; MMRM model: LS mean=-2.07 mg/dL, p<0.0001).

Additional efficacy endpoint: For the non-inferiority analysis, data were transformed on the logarithmic scale. Consequently, all data are expressed as geometric means, and changes in parameter levels between Baseline and Week 12 are expressed as geometric least square mean (GLSM) ratios.

Change from baseline in Serum P from study baseline to Week 12

From Study-baseline to Week 12, the mean reduction in serum P was similar for patients treated with KRX-0502 (−2.02 mg/dL), all active controls (−2.22 mg/dL), and sevelamer as a single agent (−2.21 mg/dL) with no significant treatment difference between KRX-0502 and all active controls (p=0.65), and KRX-0502 and the sevelamer subgroup (p=0.47) (see Table 9).

Table 9: Serum P (mg/dL) Change From Baseline to Week 12 – Efficacy Analysis Population (ANCOVA)

	All Active Controls	KRX-0502	Sevelamer Carbonate
n	146	281	78
Mean (SD) at Baseline	7.56 (1.74)	7.41 (1.63)	7.46 (1.63)
Mean (SD) at Week 12	5.34 (1.65)	5.38 (1.51)	5.25 (1.65)
Mean (SD) change from baseline	−2.22 (2.13)	−2.02 (1.998)	−2.21 (2.18)
p-value[a] for treatment difference	0.65		
		0.47	

Sources: Table 14.2.23.1 and Table 14.2.24.1.
[a] The p-value for treatment difference for the change in serum phosphorus was calculated via ANCOVA model with terms for treatment group, study baseline value, weeks post-baseline, and treatment by weeks post-baseline interaction. Between-treatment difference was calculated as LS Mean (KRX-0502) − LS Mean (active control).
Note: Only subjects with both baseline and post-baseline observations for the parameter of interests were included.
CI=confidence interval; LS=least squares; n=number of subjects; SD=standard deviation.

- Non-inferiority vs. Sevelamer: The difference between treatment groups was estimated by the treatment ratio, which was 1.029 with a 95% CI of 0.959 to 1.104 (ANCOVA) and 1.038 with a 95% CI of 0.968 to 1.113 (MMRM).
- Non-inferiority vs. Active control: the treatment ratio was 1.016 with a 95% CI of 0.960 to 1.075 (ANCOVA) and 1.018 with a 95% CI of 0.961 to 1.078 (MMRM).

Change from baseline in Serum Ca x P product from study baseline to Week 12

From Study-baseline to Week 12, the mean reduction in Ca × P product was similar for patients treated with KRX-0502 (-17.32 mg2/dL2), all active controls (-18.58 mg2/dL2), and sevelamer as a single agent (-19.98 mg2/dL2) with no significant treatment difference between KRX-0502 and all active controls (p=0.99), and KRX-0502 and the sevelamer subgroup (p=0.52).

- Non-inferiority vs. Sevelamer: The treatment ratio was 1.019 with a 95% CI of 0.951 to 1.093 (ANCOVA) and 1.035 with a 95% CI of 0.965 to 1.110 (MMRM).

- Non-inferiority vs. Active control: The treatment ratio was 0.999 with a 95% CI of 0.945 to 1.057 (ANCOVA) and 1.008 with a 95% CI of 0.951 to 1.068 (MMRM).

Change from baseline in Serum Ca from study baseline to Week 12

From Study-baseline to Week 12, there was a small mean increase in serum Ca in patients treated with KRX-0502 (0.22 mg/dL), all active controls (0.31 mg/dL), and sevelamer as a single agent (0.12 mg/dL) with no significant treatment difference between KRX-0502 and all active controls (p=0.07), and KRX-0502 and the sevelamer subgroup (p=0.85).

- Non-inferiority vs. Sevelamer: The treatment ratio was 0.998 with a 95% CI of 0.980 to 1.016 (ANCOVA) and 1.001 with a 95% CI of 0.983 to 1.019 (MMRM)
- Non-inferiority vs. Active control: the treatment ratio was 0.986 with a 95% CI of 0.971 to 1.001 (ANCOVA) and 0.990 with a 95% CI of 0.974 to 1.005 (MMRM).

ANCOVA analysis indicated that in KRX-0502 group change from baseline to week 12 in serum P, P xCa product, and Ca was non-inferior to sevelamer carbonate and to active control group. ANCOVA analysis indicated that the mean serum P_i, Ca × P products, and Ca was non-inferior to sevelamer carbonate and to active control group when compared from baseline to Week 12.

Secondary and exploratory endpoints

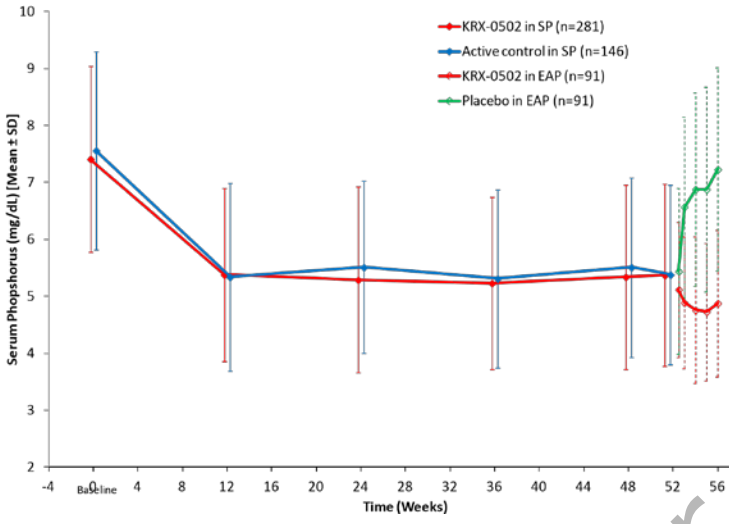
Serum P levels over time: The serum P_i data from Study 304 indicate that KRX-0502 was persistently effective in lowering serum P_i levels throughout the 52-week SP compared to active control and continued to maintain serum P_i levels from the Week-52-baseline to Week 56 in the placebo-controlled EAP (see Table 9 and Figure 7). The average daily dose needed to maintain subjects (mean BW: 90 to 97 kg) within the target P_i range was ~7 to 9 g/day.

Table 9: Serum P Change From Baseline During Study 304 – Efficacy Analysis Population

Timepoint	Safety Assessment Period	
	KRX-0502	**Active Control**
n	281	146
Baseline, mean (SD)	7.41 (1.63)	7.56 (1.74)
Change from Baseline, mean (SD)		
Week 12	−2.02 (2.00)	−2.22 (2.13)
Week 24	−2.12 (1.97)	−2.05 (2.14)
Week 36	−2.18 (1.93)	−2.25 (2.05)
Week 48	−2.07 (1.97)	−2.05 (2.07)
Week 52[a]	−2.03 (1.97)	−2.18 (2.25)
	Efficacy Assessment Period	
	KRX-0502	**Placebo**
n	91	91
Week-52 Baseline, mean (SD)	5.12 (1.19)	5.44 (1.46)
Change from Week 52-Baseline, mean (SD)		
Week 53	−0.20 (1.09)	1.17 (1.31)
Week 54	−0.33 (1.17)	1.43 (1.68)
Week 55	−0.39 (1.15)	1.44 (1.84)
Week 56[b]	−0.24 (1.26)	1.79 (1.77)

[a] Exploratory analysis endpoint. [b] Primary efficacy endpoint n=number of observations in a category; SD=standard deviation.

Figure 7 : Serum P Profile during Study 304 – Efficacy Analysis Population



Responder analysis: During the 52-week SP, the proportion of subjects achieving the serum P_i goal of ≤ 5.5 mg/dL was similar between treatments (62.3% and 63.0% for KRX-0502 and active control, respectively). At various time points (Weeks 12, 24, 36, 48 and 52), proportion of subjects achieving the serum P_i ≤ 5.5 mg/dL ranged from 60.9 to 64.8% for KRX-0502, and from 58.2 to 63.7% for active control; differences between groups were not statistically significant at any time point.

At the end 4-week EAP (week 56), significantly higher proportion of KRX-0502 recipients had serum Pi ≤ 5.5 mg/dL at the end of treatment (Week 56) compared to Placebo recipients (71.4% vs. 20.9%, respectively; p<0.0001, 95% CI [38.06, 63.03]). During the EAP, KRX-0502 recipients were significantly less likely (2.2% vs. 23.1%) to have P ≥9.0 mg/dL vs. with placebo recipients (mean proportion difference -20.88%, 95% CI [-30.04, -11.71], p <0.0001).

Iron-related parameters: Ferritin and TSAT increased significantly with KRX-0502 compared to active control. Ferritin showed a 302.08 ng/mL increase from baseline to the end of treatment in the KRX-0502 group vs. 26.37 ng/mL increase in the active control group. After the initial increase in ferritin and TSAT in the KRX-0502 group, levels plateaued for the remainder of the 52-week SP. Using the Wilcoxon Rank Sum Test, at week 52 (1) KRX-0502 recipients had a significantly lower median cumulative IV iron administration compared with active control recipients (1.87 vs. 3.83 mg/day, respectively; P <0.0001); (2) KRX-0502 recipients had a significantly lower median cumulative ESA administration compared with active control recipients (755.80 vs. 993.46 units/day, respectively; P =0.0473).

Serum iron levels increased in the KRX-0502-treated subjects to about Week 12 or 24 and then remained generally constant until Week 52 when the percentage change from baseline was 15.5 µg/dL (vs. 0.5 µg/dL in the active control group). TIBC levels decreased during the first 12 weeks of KRX-0502 treatment and then were constant for the remainder of the study (8.45 µg/dL decrease from baseline to the end of treatment versus 7.67 µg/dL increase in the active control group). Haemoglobin (Hgb) stayed relatively stable during the 52-week treatment period in KRX-0502 subjects, whereas there was a progressive slow decrease in Hgb in the active control group, with the mean Hgb significantly higher in the KRX-0502 group compared with the active control group at Weeks 12, 36, and 52.

Other exploratory parameters: Data related to changes in electrolytes indicate that the mean serum P, Ca × P products, and serum bicarbonate were not different between the KRX-0502 and active control groups at any time point. The mean serum Ca differed between the KRX-0502 and active control groups only at Week 36, with

serum Ca lower in the KRX-0502 group. iPTH was not different intheKRX-0502 group compared with the active control group at any time point. Data related to changes in vitamin levels did not reveal a particular pattern. The mean serum vitamin B-12, vitamin E, and folic acid were not different in the KRX-0502 group compared with the active control group at any time point, and a few vitamin levels differed only at a few time points. Compared with the active control group, in theKRX-0502 group 25-dihydroxy-vitamin D3 was higher at Week12, vitamin was lower at Weeks 12 and 36, and vitamin K was higher at Week 36. Data related to changes in the lipid panel indicate that the mean LDL was higher in theKRX-0502 group vs. the active control at every time point. HDL was lower in the KRX-0502 group vs. the active control at Week 36 but not at Weeks 12 and 52. Triglycerides were not different in the KRX-0502 group vs. the active control at any time point.

In conclusion, in Study 304 there were no differences in changes between baseline and Week 52 values between KRX-0502 and active control for:

Parameter Study 304 Mean (SD)	**KRX-0502 Change baseline to Week 52**	**Active Control Change baseline to Week 52**	**P value between group**
Calcium (mg/dl)	0.21 (0.88)	0.27 (0.94)	0.21
Calcium*Phosphorus	-17 (18)	-18, (20)	0.91
iPTH (pg/ml)	-170 (402)	-147 (305)	0.97
25-Dihydroxy-Vitamin D3 (ng/ml)	-1.2 (11)	- 2 (8)	0.73
Vitamin A (µg/ml)	0.2 (26)	-0.4 (32)	0.79
Vitamin B-12 (pg/ml)	-39 (1560)	-29 (430)	0.24
Vitamin E (mg/L)	0.7 (4)	0.7 (5)	0.92
Vitamin K (ng/ml)	0.15 (1)	0.02 (0.9)	0.26
Folic acid (ng/ml)	-1.5 (6)	-1.8 (7)	0.75
HDL (mg/dl)	-0.5 (7)	0.3 (8)	0.42
Triglycerides (mg/dl)	5 (120)	7 (123)	0.82

Among the 13 biological parameters followed, only LDL change was significantly different between KRX-0502 and the active control either calcium carbonate or sevelamer carbonate.

Study 204

All seven efficacy endpoints (2 primary and 5 secondary) were adjusted for multiplicity using a gatekeeping sequential strategy to control overall Type I error rate at 5%. Statistical testing of each endpoint was for the difference vs. placebo in the least squares (LS) mean change from baseline to Week 12. The pre-specified sequential testing order and the resulting p-value for each endpoint are summarized in Table 10. All endpoints with exception of eGFR (which was not statistically different from placebo) represent statistically significant improvements for KRX-0502 vs. placebo.

Table 10: Sequential Testing Order and Resulting P-Value for 7 Pre-Specified Primary and Secondary Efficacy Endpoints (ANCOVA Method; ITT Population)

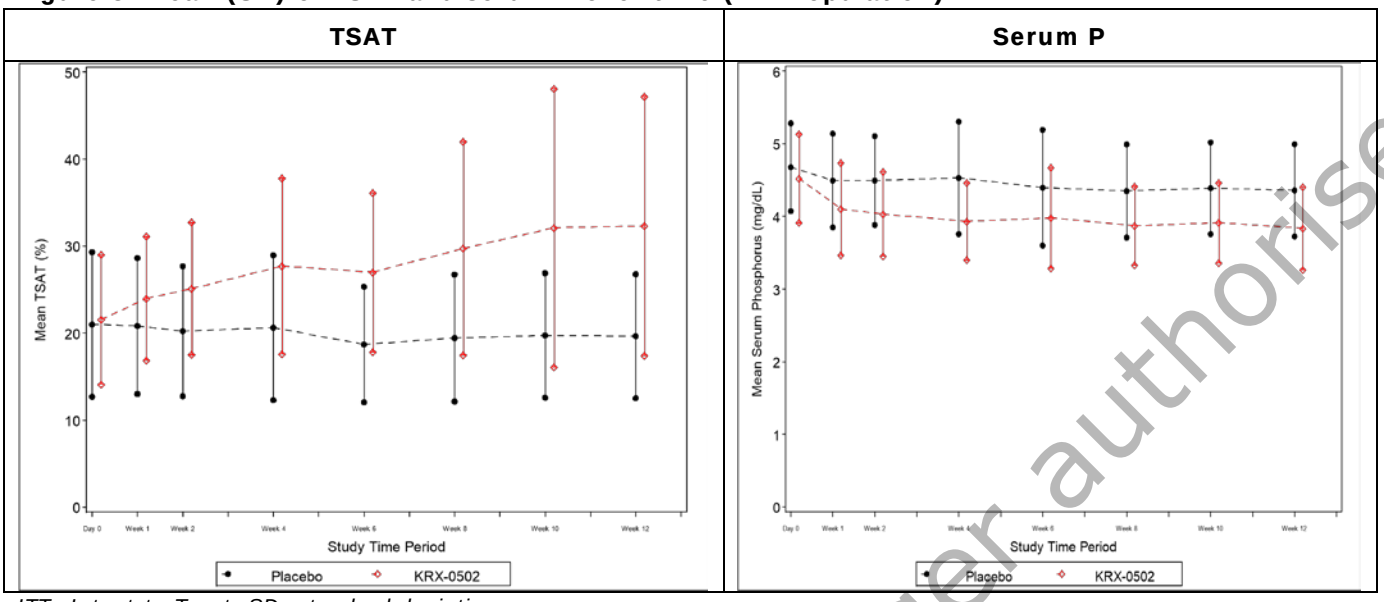
Efficacy Endpoint[a]	Statistic	Treatment Difference[a]
Primary		
Transferrin saturation, %	LS mean (SE) P-value	11.3 (1.70) <0.001
Serum phosphorus, mg/dL	LS mean (SE) P-value	-0.5 (0.10) <0.001
Secondary		
Ferritin, ng/mL	LS mean (SE) P-value	77.5 (10.83) <0.001
Hemoglobin, g/dL	LS mean (SE) P-value	0.6 (0.14) <0.001
Intact fibroblast growth factor 23, pg/mL	LS mean (SE) P-value	-125 (52.42) 0.017
Urinary phosphorus, mg per 24 hours	LS mean (SE) P-value	-287 (47.15) <0.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	LS mean (SE) P-value	-1.9 (1.11) 0.079

[a] All endpoints and results represent mean change from baseline to Week 12 for KRX-0502 compared to placebo.
Note: The efficacy variables were analyzed using an ANCOVA model with treatment as a fixed effect and baseline value as the covariate.
ANCOVA=analysis of covariance; ITT=Intent-to-Treat; LS=least squares; SE=standard error.

Co-Primary efficacy endpoints

At Week 12, mean TSAT values were significantly increased from baseline with KRX-0502 compared with Placebo: the LS mean (SE) change from baseline for the KRX-0502 and placebo groups was 10.2% (1.18%) and -1.1% (1.20%), respectively (ANCOVA, p<0.001) (see Figure 8). There was a significantly greater decrease in serum Pi with KRX-0502vs. Placebo: the LS mean (SE) change from baseline for the KRX-0502 and the placebo groups was −0.7 (0.07) mg/dL and −0.2 (0.07) mg/dL, respectively (ANCOVA, p<0.001) (see Figure 8). The treatment difference between the two groups in both of these parameters was clinically meaningful and highly statistically significant (LS mean (SE) TSAT 11.3 (1.7) % and phosphorus −0.5 (0.10) mg/dL, p<0.001). In addition, a post hoc analysis demonstrated that a higher proportion of KRX-0502-treated subjects had a sPi ≤ 4.0 mg/dL at the end of treatment (69.4% vs 27.5% with placebo).

Figure 8: Mean (SD) of TSAT and serum P over time (ITT Population)



ITT=Intent-to-Treat; SD=standard deviation.

Secondary endpoints

Secondary endpoints changed from Baseline to Week 12 in the expected favourable direction following treatment with KRX-0502. Ferritin increased from a mean (SD) baseline value of 116 (83) ng/mL to 189 (122) ng/mL at Week 12 with KRX-0502 and decreased from a baseline value of 110 (81) ng/mL to 106 (94) ng/mL at Week 12 with Placebo (mean change of 73.5 ng/mL for KRX-0502 vs. −4.4 ng/mL for Placebo). Hgb increased by 0.4 (0.8) g/dL with KRX-0502 and decreased by -0.2 (0.9) g/dL with Placebo; the treatment difference for both these parameters was significant (ANCOVA, $p<0.001$). Both intact FGF-23 and urinary P excretion decreased with KRX-0502 and increased with placebo; the treatment difference was significant for both parameters (ANCOVA, $p=0.017$ and $p<0.001$, respectively). There was no difference in the eGFR between the two treatment groups (ANCOVA, $p=0.079$).

The supportive and exploratory endpoints

There was a significant difference at Week 12 in change from baseline between the KRX-0502 group and the placebo group for the following supportive and exploratory efficacy endpoints: serum Ca × P product, serum carbon dioxide/bicarbonate, UIBC and TIBC, serum iron, HCT, and C-Terminal FGF-23. There was no statistically significant difference between the KRX-0502 group and the placebo group for the supportive and exploratory endpoints of serum Ca, urinary Ca, and iPTH.

- **Ancillary analyses**

Study 204: Supportive sensitivity analyses were performed for the primary efficacy endpoint and the secondary efficacy endpoints by longitudinal data analysis. These analyses were based on MMRM methods. All follow-up observations were utilized; missing values remained as missing, i.e., no attempt was made to impute missing values, and only observed values were used in the data analysis. The model included terms for treatment group, baseline value, weeks post baseline, and treatment by weeks post-baseline interaction.

Results of sensitivity analyses for both primary endpoints using the MMRM method confirmed the results by ANCOVA at Week 12. In addition, the mean changes from baseline in subjects from the KRX-0502 group were

significantly different from those in subjects from the placebo group at every time point assessed, beginning with the first assessment at Week 1. Results of a sensitivity analysis using the MMRM method for all secondary efficacy endpoints at Week 12 were similar to results by ANCOVA.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11. Summary of efficacy for trial Study 304

Title: A Three-Period, 58-Week Safety and Efficacy Trial of KRX-0502 (ferric citrate) in Patients with End-Stage Renal Disease (ESRD) on Dialysis		
Study identifier	KRX-0502-304	
Design	It was a Phase 3, multicenter, randomized, open-label, active-controlled and then placebo-controlled study in subjects with CKD on thrice-weekly dialysis (HD or PD) receiving treatment for hyperphosphataemia, which evaluated the safety and efficacy of KRX-0502 1-g tablets administrated TID with a starting dose of 6 g/day, titrated depending on serum phosphorus levels up to 12 g/day. The design included: 1) a washout period of up to 2 weeks followed by 2) a 52-week safety assessment period (SP) (comparing KRX-0502 to active controls of sevelamer carbonate and/or calcium acetate) and then 3) a 4-week efficacy assessment period (EAP) (comparing KRX-0502 to placebo in the patients assigned to KRX-0502 who successfully completed the safety assessment period).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 weeks 2 weeks NA
Hypothesis	Superiority (against placebo, primary endpoint) and Non-inferiority (against sevelamer; additional efficacy endpoint)	
Treatments groups	KRX-0502 (dose titration, SP)	Starting dose: 6 g/day TID, titrated to a maximum daily dose of 12 g/day to achieve the target serum Pi of 3.5 to 5.5 mg/dL. Permitted doses: 0–12 g/day. Duration: baseline–Week52 N=292
	Active control (sevelamer carbonate, calcium acetate or both) (dose titration, SP)	Starting doses: were based on the last dose administered before Washout Period or at the discretion of the PI; titration was according to the package inserts, and/or at the discretion of the PI; Duration: baseline–Week52. N=149
	KRX-0502 (dose titration, EAP)	Starting dose: the same as on Week 52, titrated to a maximum daily dose of 12 g/day to achieve the target serum Pi of 3.5 to 5.5 mg/dL. Permitted doses: 0–12 g/day. Duration: Week52–Week 56. N=96
	Matching placebo (dose titration EAP)	Dosing the same as with KRX-0502 during EAP. Duration: Week52–Week 56. N=96

Endpoints and definitions	Primary endpoint	Efficacy	Change in serum Pi from Week-52-baseline to the end of EAP (Week 56)
	Additional efficacy endpoint	Efficacy	Non-inferiority vs. sevelamer carbonate in terms of change in serum Pi from baseline to Week 12
	Secondary endpoints	Efficacy	(1) change in serum ferritin and TSAT from Baseline to Week 52; (2) cumulative IV iron and ESA administration use compared to the active control from randomization to Week 52;
Database lock	Not provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis population Week52-Week56		
Descriptive statistics and estimate variability	Treatment group	KRX-0502	Placebo
	Number of subject	91	91
	Serum P_i, mg/dL, LS mean	-0.24	1.79
	SD	1.255	1.767

Effect estimate per comparison	Primary endpoint	Comparison groups	KRX-0502 vs. Placebo
		Difference in LS means*, mg/dL	−2.18
		95% CI	-2.59, -1.77
		P-value	<0.0001
Notes	* The LS mean treatment difference and P-value for the change in mean serum phosphorus were calculated via an ANCOVA model with treatment as the fixed effect and Week-52-baseline as the covariate. Between-treatment differences were calculated as the LS mean (KRX-0502) – LS mean (placebo).		

Analysis description	**Additional efficacy analysis (primary for EMA)**		
Analysis population and time point description	Full analysis population Baseline-Week12		
Descriptive statistics and estimate variability	Treatment group	KRX-0502	Sevelamer
	Number of subject	281	78
	Serum P_i, mg/dL, geometric LS mean	-2.02	-2.21
	SD	1.998	2.18

Effect estimate per comparison	Additional efficacy endpoint	Comparison groups	KRX-0502 vs. Sevelamer
		Difference treatment ratio*, mg/dL	1.029
		95% CI	0.959, 1.104
		P-value	0.47
Notes	* Estimated from an ANCOVA on the logarithmic scale with baseline as covariate. LOCF was used to impute missing data.		

Table 12. Summary of efficacy for trial Study 204

Title: A Phase 2 Study of KRX-0502 (ferric citrate) in Managing Serum Phosphorus and Iron Deficiency in Anemic Subjects with Stage III to V Chronic Kidney Disease Not on Dialysis				
Study identifier	KRX-0502-204			
Design	It was a Phase 2, randomized, placebo-controlled, double-blind study of KRX-0502 in *non-dialysis* subjects with CKD stage 3-5 and iron deficiency anaemia. The design included: 1) a 2-week washout period followed by 2) a *12-week treatment period* (comparing KRX-0502 with placebo).			
	Duration of main phase:	12 weeks		
	Duration of Run-in phase:	2 weeks for subjects on phosphate binders; no Run-in phase for *de novo* subjects		
	Duration of Extension phase:	NA		
Hypothesis	Superiority (against placebo, primary endpoint)			
Treatments groups	KRX-0502 (dose titration)		Starting dose: 3 g/day TID, titrated to a maximum daily dose of 12 g/day to achieve the target serum Pi of 3.0 to 3.5 mg/dl. Permitted doses: 0–12 g/day. Duration: baseline–Week12 N=75	
	Matching placebo (dose titration)		Dosing the same as with KRX-0502. Duration: baseline–Week12. N=74	
Endpoints and definitions	Co-Primary endpoints	Efficacy	Changes in TSAT and serum P from baseline to the end of the 12-week Treatment Period	
	Secondary endpoints	Efficacy	Change from baseline in Ferritin, Hgb, Intact FGF-23, Urinary phosphorus, and eGFR at Week 12.	
Database lock	Not provided			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intended-to-treat (ITT) population Baseline-Week12			
Descriptive statistics and estimate variability	Treatment group		KRX-0502	Placebo
	Number of subject		72	69
	Serum P_i, mg/dL, LS mean		-0.7	-0.3
	SD		0.61	0.74
	Serum TSAT, %, LS mean		10.2	-1.1
	SD		1.18	1.20
Effect estimate per comparison	Co-Primary endpoint	Comparison groups		KRX-0502 vs. Placebo
	Serum P_i	Difference in LS means (SE), mg/dL		-0.5 (0.10)
		95% CI		-0.7, -0.3

		P-value	<0.001
	Serum TSAT	Difference in LS means (SE), %	11.3 (1.70)
		95% CI	8.0, 14.7
		P-value	<0.001
Notes	The efficacy variables were analyzed using an ANCOVA model with treatment as a fixed effect and baseline value as the covariate.		

Clinical studies in special populations

No studies in children or patients with hepatic impairment were performed. As regards the elderly, the age range of patients enrolled in studies 304 and 204 was 19-90 and 22-88, respectively. In a subgroup analysis performed for study 304, there was no notable difference by age group in the primary efficacy endpoint analysis. Across all 3 age groups, serum Pi remained relatively stable from Week 52-baseline to Week 56, and the treatment differences relative to Placebo were generally similar and statistically significant despite the small sample sizes in the older age groups.

Analysis performed across trials (pooled analyses AND meta-analysis)

The study design elements varied sufficiently across these studies such that a formal pooled analysis of efficacy was not considered feasible or clinically relevant by the Applicant.

Supportive studies

Subgroup analysis: The applicant analyzed KRX performances for efficacy in several important sugroups: age (< 65 years; 65 to < 75 years; ≥ 75 years), weight (≤ 65, > 65 to ≤ 95 and > 95 kg), type of dialysis (HD vs PD), race (Caucasian; African-American; Asian), Baseline sP levels (< 7mg/dl; > 7 mg/dl), and type of P binder at the screening (sevelamer of Calcium based). Broadly, the efficacy result in subgroups showed some differences that were expected (1) higher effect in case of lower body weight, higher baseline sP level, if patient were switched from Sevelamer as compared to from Calcium based treatments) and (2) comparable in others (gender, diabetes status). At the same time trends in increased effect by age is somewhat unexpected (mean decrease by -2.02 vs -2.30 vs -2.92 mg/dL in age < 65 vs. 65 to < 75 vs. ≥ 75 years, respectively).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The two pivotal trials 304 and 204 were multicenter, randomized studies. Blinding measures for primary efficacy analyses were employed. Study 304 was open-label phase 3 study in CKD 5D subjects, which consisted active-controlled period, followed by placebo-controlled period. Study 204 was double blind, placebo controlled, 3-period phase 2 study in CKD ND subjects. Study 304 was continuing as long term (up to 48-week) open-label safety extension study 307. Design for one pivotal study in HD population supported with second study can be accepted for consistency assessment in highly similar population (non-dialysis). Two main studies included clinically relevant hyperphosphatemic populations representing mixed both HD and non-HD settings.

In study 304, the primary efficacy objective was to determine the efficacy of KRX-0502 as a treatment for hyperphosphataemia in a 4-week EAP in subjects with ESRD who were undergoing either HD or PD. The alternative primary efficacy objective (primary for European Medicines Agency) was to determine the non-inferiority of KRX-0502 as a treatment for hyperphosphataemia at Week 12 vs sevelamer carbonate in SP

population. In study 204, objectives were to compare the efficacy and safety of KRX-0502 to placebo in managing serum P and iron deficiency anaemia in subjects with Stage 3 to 5 CKD ND as measured by changes in TSAT and serum P over a 12-week Treatment Period. The sample sizes are sufficient to detect the difference between placebo for HD population (delta of ≥1.2 mg/dL and for non-HD population (delta of ≥0.3 mg/dL) as it was planned and provide additional information for safety. The baseline demographics and medical history was more or less balanced between treatment groups as far as the analysis was performed. Protocol amendments performed and protocol deviations are not considered to affect the robustness of the data.

Efficacy data and additional analyses

Administration of KRX-0502 maintained serum P_i from Week 52 to Week 56 (mean change of –0.24 mg/dL in ANCOVA model using LOCF, and -0.23 mg/dL in MMRM model) whereas the serum P_i increased in the Placebo group (mean change of 1.79 mg/dL 95% CI [1.57, 2.15] in ANCOVA model using LOCF, and 1.46 mg/dL, 95% CI [1.49, 2.11] in MMRM model) in Full analysis population. Serum P_i was significantly lower in the KRX-0502 group vs. Placebo group at Week 56 (ANCOVA model using LOCF: LS Mean = −2.18 mg/dL; p<0.0001; MMRM model: LS mean=-2.07 mg/dL, p<0.0001). From Study-baseline to Week 12, the mean reduction in serum P was similar for patients treated with KRX-0502 (−2.02 mg/dL), all active controls (−2.22 mg/dL), and sevelamer as a single agent (−2.21 mg/dL) with no significant treatment difference between KRX-0502 and all active controls (p=0.65), and KRX-0502 and the sevelamer subgroup (p=0.47).

The NI vs. Sevelamer: The difference between treatment groups was estimated by the treatment ratio, which was 1.029 with a 95% CI of 0.959 to 1.104 (ANCOVA) and 1.038 with a 95% CI of 0.968 to 1.113 (MMRM).

The NI vs. Active control: the treatment ratio was 1.016 with a 95% CI of 0.960 to 1.075 (ANCOVA) and 1.018 with a 95% CI of 0.961 to 1.078 (MMRM).

Responder analysis: At the end of the 4-week EAP (week 56), significantly higher proportion of KRX-0502 recipients had serum Pi ≤ 5.5 mg/dL at the end of treatment (Week 56) compared to Placebo recipients (71.4% vs. 20.9%, respectively; p<0.0001, 95% CI [38.06, 63.03]). During the EAP, KRX-0502 recipients were significantly less likely (2.2% vs. 23.1%) to have P ≥9.0 mg/dL vs. with placebo recipients (mean proportion difference -20.88%, 95% CI [-30.04, -11.71], p <0.0001). During the 52-week SP population observation, the proportion of subjects achieving the serum P_i goal of ≤ 5.5 mg/dL was similar between treatments (62.3% and 63.0% for KRX-0502 and active control, respectively). At various time points (Weeks 12, 24, 36, 48 and 52), proportion of subjects achieving the serum P_i ≤ 5.5 mg/dL ranged from 60.9 to 64.8% for KRX-0502, and from 58.2 to 63.7% for active control; differences between groups were not statistically significant at any time point.

Efficacy in non-dialysis population: The levels of sP constantly decreased more (by ~–0.5 mg/dL) for the studied population in KRX-0502 as compared to placebo group (~-0.7 vs. ~-0.2). The applicant analyzed KRX performances for efficacy in several important subgroups: age (< 65 years; 65 to < 75 years; ≥ 75 years), weight (≤ 65, > 65 to ≤ 95 and > 95 kg), type of dialysis (HD vs PD), race (Caucasian; African-American; Asian), Baseline sP levels (< 7mg/dl; > 7 mg/dl), and type of P binder at the screening (sevelamer of calcium based). Broadly, the efficacy result in subgroups showed some differences that were expected (1) higher effect in case of lower body weight, higher baseline sP level, if patient were switched from sevelamer as compared to from calcium based treatments) and (2) comparable in others (gender, diabetes status).

A number of other secondary efficacy endpoints were tested that support the lowering sP effect and suggest parallel iron supplementation (at least from the study 204, where no IV iron products was used). The clinical advantage of this effect was not supported by the CHMP due to the increased risk of iron overload particularly in patients requiring high doses of Fexeric because of high hyperphosphataemia, but not requiring iron supplementation because of lower iron demand, such as men, non dialysis patients, patients on peritoneal

dialysis and patients without iron depletion either pre-treatment or during treatment. The inclusion of iron supplementation into the indication was therefore not pursued by the applicant and instead, an appropriate warning statements on possible iron overload were included in the SmPC. The treating physicians are furthermore advised in the product information to monitor iron parameters and to discontinue Fexeric in case of ferritin exceeding 800 ng/ml.

2.5.4. Conclusions on the clinical efficacy

The results of the main efficacy studies demonstrate that KRX-0502, taken in divided doses during meals at starting doses of 3 to 6 g/day and titrated based on serum Pi levels up to a maximum of 12 g/day, is effective for the control of hyperphosphataemia in adult CKD patients both Stage 5 undergoing HD and PD or in CKD-ND. The claim for iron supplementation in the indication was not supported due to questionable clinical value and safety considerations particularly in patients requiring high doses of Fexeric because of high hyperphosphatemia but not requiring iron supplementation because of lower iron demand, such as men, non dialysis patients, patients on peritoneal dialysis and patients without iron depletion either pre-treatment or during treatment.

2.6. Clinical safety

Patient exposure

The evaluation of safety is based on 18 studies: 1 Phase 1study, 1 Phase 2a study, 7 Phase 2 studies and 9 Phase 3 studies. Overall, the clinical trials included 1947 unique subjects (see Table 13). There were 1533 subjects exposed to ferric citrate, 330 to active control and 262 to placebo. Among the 1533 subjects exposed to ferric citrate, there were 1388 subjects with CKD 5D and 145 subjects with CKD ND. A total of 166 patients were included to the long-term safety study 307. As of 15 October 2013, 659 subjects have received treatment with ferric citrate for ≥6 months, 378 for ≥1 year, and 29 subjects have completed 2 years (>96 weeks) of treatment. The majority of subjects received titrated doses rather than fixed doses.

Table 13. Treatment exposure relevant to safety evaluation (all studies)

Phase	Study	Ferric Citrate			Active Control	Placebo	Total
		KRX-0502	JTT-751	Ferric Citrate[a]			
Pooled Safety Set – Subjects With CKD on Dialysis							
Phase 3	Study 304	292[b]	—	—	149[b]	95[c]	438[d]
Phase 3	Study 305	151[e]	—	—	—	—	151
Phase 2	PBB00101	100	—	—	—	16	116
Phase 2	Study 201	55	—	—	—	—	55
	Total	**557**[b]	—	—	**149**[b]	**111**[c]	**704**[d]
Supportive Studies – Subjects With CKD on Dialysis							
Phase 2	Study GBA2-1	—	144	—	—	48	192
Phase 2	Study GBA2-2	—	10	—	—	—	10
Phase 3	Study GBA4-1	—	116	—	113[f]	—	229
Phase 3	Study GBA4-3	—	56	—	—	—	56
Phase 3	Study GBA4-5	—	234	—	—	—	234
Phase 3	Study GBA4-6	—	180	—	—	—	180
	Total	—	**740**	—	**113**[f]	**48**	**901**
Non-Dialysis Studies							
Phase 2	Study 204	75	—	—	—	73	148
Phase 3	GBA4-4	—	59[g]	—	—	30	89
Phase 3	GBA4-7	—	29[h]	—	—	—	29[h]
	Total	**75**	**70**[g,h]	—	—	**103**	**237**[h]
Other Supportive Studies							
Phase 2	Study 202	22	—	—	—	—	22
Phase 2	Open-Label Extension (Taiwan)	28[k]	—	—	—	—	28[k]
	Total	**23**					**23**[k]
Preliminary Studies							
Preliminary	Univ. of Michigan Study 1	—	—	54[i]	54[i]	—	54[i]
Preliminary	Univ. of Michigan Study 2	—	—	14[j]	14[j]	—	28[j]
	Total	—	—	**68**	**68**	—	**82**[i,j]
	TOTAL	**655**[k,l]	**810**	**68**	**330**[i]	**262**	**1947**
	TOTAL FERRIC CITRATE		**1533**[l]				

[a] Commercial ferric citrate was used in Univ. of Michigan Study 1 and Univ. of Michigan Study 2.
[b] A total of 56 subjects (both KRX-0502 and active control groups) from Study 305 were enrolled into Study 304. Therefore, of the 292 subjects randomized in the KRX-0502 group, 251 were unique subjects (41 were enrolled from Study 305). In addition, although the counts in this table and the Pooled Safety Set are based on the number randomized, 3 randomized subjects were never treated, so the Safety Population included 289 subjects. In addition, there were 3 subjects randomized to KRX-0502 in the EAP who had switched from Active Control during the SP, included in the total count of 557. Of the 149 subjects treated in the Active Control group (sevelamer carbonate, calcium acetate, or both), 134 were unique subjects (15 were enrolled from Study 305).
[c] All 95 subjects who received placebo in the Efficacy Assessment Period of Study 304 had completed 52 weeks of treatment with KRX-0502 in the Safety Assessment Period.
[d] As defined in Footnotes b and c, of the 441 subjects randomized in Study 304, 382 unique subjects participated in Study 304, and in the count of KRX-0502 treated subjects, 3 were switchers from active control in the SP.
[e] Of the 151 subjects, 51 subjects were exposed to 1 g/day, 52 subjects were exposed to 6 g/day, and 48 subjects were exposed to 8 g/day of ferric citrate.
[f] Subjects were randomized to receive sevelamer hydrochloride.
[g] A total of 60 subjects received JTT-751; however, 1 subject was discontinued from the study due to erroneous administration of the study drug and was excluded from the safety analysis.
[h] All 29 subjects in Study GBA4-7 had completed Study GBA4-4; 18 had received JTT-751 during GBA4-4 and are thus not counted again in the total rows.
[i] Subjects were randomized to receive either calcium carbonate or ferric citrate for 4 weeks followed by a 2-week washout period and then crossed over to receive the alternate treatment for 4 weeks.
[j] Subjects were randomized into 2 groups: calcium acetate or ferric citrate.
[k] All but 1 of the subjects in the OLE study had previously participated in Study PBB00101 and had received KRX-0502/ferric citrate.
[l] An additional 52 subjects were exposed to KRX-0502 in the ongoing Study 307, who were previously treated with Active Control in Study 304.

CKD=chronic kidney disease; OLE=Open-label Extension of PBB00101; Univ=university.

Safety data were analysed for the safety population, defined as all subjects who took at least 1 dose of study drug. The primary safety evaluation focuses on the integrated data from (1) 4 studies in CKD 5D patients (Pooled Safety Set [PSS]), and (2) 1 study in CKD ND subjects (study 204). PSS consists of 704 subjects; studies varied in design, dose, and treatment duration. Extent of exposure is summarised in Table 14. Exposure to KRX-0502 in the pivotal study 304 was significantly longer (52 weeks in the SP followed by 4 weeks in the EAP) compared to the other 3 studies in the PSS (4 weeks each).

Table 14. Study drug exposure in PSS

Category	All KRX-0502 (N=557)	Active Control (N=149)
Duration of exposure (weeks)		
n	557	149
Mean (SD)	24.52 (24.089)	45.04 (15.383)
Median (Min, Max)	4.86 (−2.4, 60.9)	52.14 (−2.3, 62.6)
Duration of exposure by category, n (%)		
≤12 weeks	303 (54.4%)	12 (8.1%)
>12 to 24 weeks	21 (3.8%)	10 (6.7%)
>24 to 36 weeks	19 (3.4%)	6 (4.0%)
>36 to 48 weeks	13 (2.3%)	7 (4.7%)
>48 weeks	201 (36.1%)	114 (76.5%)
Total Person Time (months)	3142.98	NR
Average prescribed dose per day (g/day)		
n	557	147
Mean (SD)	6.14 (2.817)	5.78 (2.149)
Median (Min, Max)	6.00 (1.0, 12.0)	5.30 (1.3, 9.6)
KRX-0502 dose, n (%)		
<6 g/day	192 (34.5%)	—
≥6 to <9 g/day	285 (51.2%)	—
≥9 g/day	80 (14.4%)	—

Sources: ISS, Table 2.1.1, Table 3.20.2
Max=maximum; Min=minimum; N=number of subjects in the treatment group (denominator for percentages); n=number of subjects in the subset (numerator for percentages); SD=standard deviation; NR=not reported.

The comparison of the demographic characteristics in a PSS population did not show meaningful differences between the treatment groups. Demographic characteristics were balanced across dose groups and across duration of exposure. The racial distribution and body weight in the PSS reflected the US location of the studies. Across the three treatment groups, the majority of subjects were Black (51.4% to 52.4%). There were 190 White subjects in KRX-05-02 group (34.1%); in active control and placebo groups there were 62 (41.6%) and 43 (38.7%) White subjects, respectively. The mean weight at baseline ranged from 89.5 to 94.1 kg. The majority of subjects across the three treatment groups were in the >65 to 95kg group (41 to 51 %). Across the studies in the PSS, significantly more subjects in the KRX-0502, active control, and Placebo groups were on haemodialysis (98.0%, 97.3%, and 95.5%, respectively) than on peritoneal dialysis (2.0%, 2.0%, and 4.5%, respectively). The majority of subjects on KRX-0502, active control, and placebo were subjects with diabetes (57.3%, 61.1%, and 62.2%). Although the presence of liver disease or dysfunction at baseline was not specifically recorded in the clinical studies, 12% (67/557), 18% (27/149) and 11% (12/111) of subjects, respectively, in the KRX-0502, active control and placebo groups were identified as having hepatic impairment at baseline, based on medical history and liver function tests. In the PSS, 99.8%, 99.3%, and 100.0% of subjects in the KRX-0502, active control, and Placebo groups, respectively, reported at least 1 concomitant medication, including sodium chloride (63.9%, 83.2%, and 74.8%), saccharated iron oxide for iron trivalent, parenteral preparations (47.4%, 75.2%, and 22.5%), paricalcitol (46.0%, 51.0%, and 41.4%), paracetamol (41.8%, 57.7%, and 58.6%), and acetylsalicylic acid (34.1%, 51.0%, and 50.5%). Among the 1533 subjects exposed to ferric citrate, there were 1388 subjects with CKD 5D and 145 subjects with CKD ND. Major part of this safety size is composed of KRX or very relevant to KRX formulation (JTT-751). Only minor part (68 patients)

constitutes by non-specific (commercial) ferric citrate formulation. Overall, 659 subjects have received treatment with ferric citrate for ≥6 months, 378 for ≥1 year, and 29 subjects have completed 2 years (>96 weeks) of treatment. The majority of subjects received titrated doses rather than fixed doses.

Adverse events

The incidence of TEAEs in Study 304 was comparable between the KRX-0502 group and the active control group during the SP (90.3% and 89.3%, respectively) and during the EAP (29.5% and 34.7%, respectively). During the SP, the most common TEAEs were in the GI disorders SOC in each treatment group. The frequency of GI disorders TEAEs was higher in the KRX-0502 group (56.4%) compared to active control group (46.3%). During the SP, the incidence of *related* TEAEs was higher in the KRX-0502 group compared with the active control group (105 [36.3%] vs. 18 [12.1%]). The most common drug-related TEAEs were associated with GI Disorders, which occurred more frequently (in 101 subjects, 34.9%) in the KRX-0502 group than in the active control group (11 subjects, 7.4%). The overall incidence of TEAEs, irrespective of relationship to study drug was comparable for the KRX-0502 (overall: 77%; Study 304: 90%) and active control (Study 304: 89%) groups. During the EAP in Study 304, the overall proportion of subjects with TEAEs was similar in the KRX-0502 (28/95; 29.5%) and placebo (33/95; 34.7%) groups. In long-term extension study 307, 85.5% of subjects experienced TEAEs. The most frequently reported TEAEs were diarrhoea (15.1%), vomiting (9.6%), nausea (9.0%), faeces discoloured (8.4%), and arteriovenous fistula site complication and headache (7.8% each). A total of 21.1% of subjects had TEAEs that were suspected to be related to study drug. The most common drug-related TEAEs occurring in ≥5% of subjects were associated with the Gastrointestinal Disorders SOC; these TEAEs occurred in 16.9% of subjects and included the PTs of faeces discoloured (8.4%) and diarrhoea (6.0%). Examination of AEs by mean dose of KRX-0502 in the PSS revealed that the frequency of subjects with at least 1 TEAE was lower in the <6 g/day group (65.1%) as compared to ≥6 to 9 g/day (81.8%) and ≥9 g/day (90.0%) groups (Table 15). The frequency of subjects with a serious or a severe TEAE was lowest in the <6-g/day group. There was no trend in the frequency of related AEs and AEs leading to study drug discontinuation. In the PSS, the majority of subjects experienced TEAEs that were mild to moderate in intensity: KRX-0502 (58.5%; 65.7% in Study 304), active control (58.4%), or placebo (33.3%). The frequency of subjects reporting at least 1 severe TEAE was higher in the active control group (30.9%) as compared to the KRX-0502 (18.7% overall and 24.6% in the SP of Study 304) group. In the PSS population, more subjects who reported at least 1 related TEAE in KRX-0502 group (37% [36% in Study 304]) than in active control group (12%).

Table 15: AEs by Treatment Group, PSS

AE Category	All KRX-0502 (N=557) n (%)	Study 304 KRX-0502 (N=289)[a] n (%)[b]	Study 304 Active Control (N=149) n (%)	Placebo (N=111) n (%)	Study 307[f] KRX-0502 (N=166) n (%)
Subjects with at least 1 TEAE	430 (77.2%)	261 (90.3%)	133 (89.3%)	44 (39.6%)	142 (85.5%)
Subjects with at least 1 related[c] TEAE	206 (37.0%)	105 (36.3%)	18 (12.1%)	4 (3.6%)	35 (21.1%)
Subjects with at least 1 severe[d] TEAE	104 (18.7%)	71 (24.6%)	46 (30.9%)	7 (6.3%)	57 (34.3%)
Subjects with at least 1 serious[e] TEAE	142 (25.5%)	114 (39.4%)	73 (49.0%)	18 (16.2%)	75 (45.2%)
Subjects who died[e]	14 (2.5%)	13 (4.5%)	8 (5.4%)	0	6 (3.6%)
Subjects with at least 1 related[c] serious[e] TEAE	6 (1.1%)	4 (1.4%)	4 (2.7%)	0	0
Subjects with TEAE leading to study drug discontinuation	67 (12.0%)	41 (14.2%)	14 (9.4%)	3 (2.7%)	19 (11.4%)

[a] *Safety Assessment Period of Study 304.*
[b] *Denominators for percentages are based on subjects in the Safety Population.*
[c] *Related includes the categories of Possibly Related, Probably Related, Related, and Suspect. Missing relation counts as related.*
[d] *Four subjects with missing severity in the KRX-0502 group were counted as severe.*
[e] *SAEs and deaths up to 30 days after discontinuation/completion of study drug are counted.*
[f] numbers for Safety population
Note: Percentages are based on the number of safety subjects within each treatment group and subgroup category.

The most frequently occurring related TEAEs by PT in the KRX-0502 group were discoloured faeces (16%), diarrhoea (16%), and constipation (5.5%), all of which are pharmacological class effects of iron-containing medicinal products (Table 16). Discoloured faeces, diarrhoea and constipation occurred at a substantially higher frequency in KRX-0502-treated subjects relative to the active control subjects in Study 304. According the Applicant, the difference may be due to the exclusion of subjects with previous intolerance to the active control agents (sevelamer carbonate and/or calcium acetate) from Study 304.

Table 16: Summary of Most Common (≥ 1% of Subjects) Related TEAEs by System Organ Class and Preferred Term, by Treatment Group

System Organ Class Preferred Term	All KRX-0502 (N=557) n (%)	Study 304 KRX-0502 (N=289)[a] n (%)[b]	Study 304 Active Control (N=149) n (%)	Placebo (N=111) n (%)
Subjects with at least 1 TEAE	**206 (37.0%)**	**105 (36.3%)**	**18 (12.1%)**	**4 (3.6%)**
Gastrointestinal Disorders	197 (35.4%)	101 (34.9%)	11 (7.4%)	4 (3.6%)
Abdominal discomfort	9 (1.6%)	5 (1.7%)	0	1 (0.9%)
Abdominal distension	8 (1.4%)	2 (0.7%)	0	1 (0.9%)
Abdominal pain	12 (2.2%)	5 (1.7%)	2 (1.3%)	0
Constipation	30 (5.4%)	16 (5.5%)	3 (2.0%)	0
Diarrhoea	70 (12.6%)	45 (15.6%)	1 (0.7%)	3 (2.7%)
Faeces discoloured	102 (18.3%)	45 (15.6%)	0	1 (0.9%)
Nausea	21 (3.8%)	10 (3.5%)	5 (3.4%)	0
Vomiting	12 (2.0%)	5 (1.7%)	2 (1.3%)	0

[a] *Safety Assessment Period.*
[b] *Denominators for percentages are based off of subjects in the Safety Population.*
Note: A subject is only counted once at each level of summarization; events can occur multiple times per subject. Results in the Study 304 column are based on the safety population.

Across the 6 supportive dialysis studies, the most frequently occurring SOCs for subjects receiving JTT-751 were GI disorders, reported in 35.0% of subjects on JTT-751 in short-term studies and 50.8% in long-term studies, infections and infestations (21.5% and 63.7%, respectively), and injury, poisoning, and procedural complications (9.5% and 34.6%, respectively). The most commonly reported (>5% in short- and long-term studies) AEs among subjects on JTT-751 were nasopharyngitis, reported in 11.7% of subjects in short-term studies and 45.7% in long-term studies; diarrhoea (14.4% and 24.9%, respectively); and constipation (5.2% and 25.8% respectively). Contusion, back pain, shunt stenosis, vomiting, excoriation, arthralgia, and eczema were reported in 5.1 to 10.6% of subjects in long-term studies and <5% (0.6% to 3.1%) in short-term studies.

The Non-Dialysis Studies included 248 subjects from Studies 204, GBA4-4, GBA4-7. The frequency of subjects on KRX-0502/JTT-751 reporting AEs was comparable in the 2 short-term (<12-week) studies (Study 204: 69.3%; Study GBA4-4: 69.5%) and higher in Study GBA4-7 (93.1%) as expected given the longer duration of treatment (>12 week). In Study 204, the majority of subjects experienced mild to moderate TEAEs in both the KRX-0502 (48/52; 92.3%) and placebo (36/43; 83.7%) groups. Severe TEAEs were reported at a higher rate in the placebo group (16.3%; 7/43) compared to the KRX-0502 group (7.7%; 4/52). In short-term studies, fewer subjects on KRX-0502/JTT-751 (32.2% and 40.0%) reported treatment-related AEs compared to the long-term study (44.8%). In placebo-controlled studies, the incidence of related AEs in subjects on KRX-0502/JTT-751 was higher than on placebo (Study 204: 40.0% vs. 17.8%, respectively; Study GBA4-4: 32.2% vs. 26.7%, respectively). The most frequents AEs by PT in non-dialysis studies are summarised in Table 17.

Table 17. AEs occurred in ≥ 5% of Subjects in the KRX-0502/JTT-751 Group in any of Non-Dialysis Studies

	Short-term (up to 12 weeks)				Long-term (>12 weeks)
	Study 204		GBA4-4		GBA4-7
Adverse Events PT	Placebo N=73 n (%)	KRX-0502 3-12 g/day N=75 n(%)	Placebo N=30 n (%)	JTT-751 1.5-6 g/day N=59 n (%)	JTT-751 (1.5-6 g/day) N=29 n (%)
Abdominal discomfort	1 (1.4%)	2 (2.7%)	3 (10.0%)	3 (5.1%)	1 (3.4%)
Abdominal distension	0	1 (1.3%)	2 (6.7%)	3 (5.1%)	3 (10.3%)
Constipation	4 (5.5%)	14 (18.7%)	3 (10.0%)	9 (15.3%)	8 (27.6%)
Cough	0	0	0	1 (1.7%)	2 (6.9%)
Diarrhoea	4 (5.5%)	15 (20.0%)	4 (13.3%)	12 (20.3%)	6 (20.7%)
Dyspepsia	0	2 (2.7%)	1 (3.3%)	0	0
Faeces discoloured	0	24 (32.0%)	0	0	0
Headache	1 (1.4%)	1 (1.3%)	0	1 (1.7%)	2 (6.9%)
Hypertension	1 (1.4%)	2 (2.7%)	1 (3.3%)	2 (3.4%)	2 (6.9%)
Nasopharyngitis	0	1 (1.3%)	1 (3.3%)	8 (13.6%)	13 (44.8%)
Nausea	5 (6.8%)	5 (6.7%)	3 (10.0%)	2 (3.4%)	0
Upper respiratory tract infection	0	4 (5.3%)	0	0	0
Vomiting	4 (5.5%)	4 (5.3%)	2 (6.7%)	1 (1.7%)	0

Sources: Study 204 CSR, Table 14.3.1.2.1; Study GBA4-4 CSR, Table 14.3.1.3; Study GBA4-7 CSR, Table 14.3.1.3

[a] Exacerbation of constipation.

N=number of subjects in the treatment group (denominator for percentages); n=number of subjects in the subset (numerator for percentages); PT=preferred term.

The frequency of reporting of several categories of AEs in the non-dialysis studies varied from the reporting in the PSS; a comparable frequency of all AEs and related AEs was reported, but there was a lower frequency of severe AEs, and SAEs.

TEAEs and ADRs in dialysis population: Primary safety information comes from PSS population for dialysis patients ((557 patients who received KRX, mainly from phase 3 study 304) and from main non-dialysis population (short term phase 2 Studies 204 and GBA4-4 and long-term Study GBA 4-7). The total primary dialysis population showed somewhat lower proportion of subjects, experiencing at least 1 TEAE as compared to active control (~77% vs. 89% in pooled 557 KRX received PPS patients vs. 149 active control patients). Although, the direct comparison with active control did show comparable TEAE rates (90.3% vs. 89.3% in all 289 KRX received patients vs. 149 active control patients in Study 304). In any case, this is higher as compared to placebo (39.6% in pooled 111 CKD HD patients from PPS population who received placebo). Consistently higher ADR rates reported in KRX received dialysis patients as compared either comparator or placebo (~37% vs. ~12% vs. 3.6% for KRX, Active comparator or placebo, respectively). These higher rates are driven mainly by GI ADRs (~34% vs. ~7% for KRX and Active comparator, respectively). Across the 6 supportive dialysis studies TEAE were clearly lower in the rates as compared to PSS population but with clear feature of time dependence (for nasopharyngitis, diarrhoea and constipation, vomiting, excoriation, arthralgia and eczema).

AESI: Several key safety concerns were associated with phosphate binding agents and/or oral iron products (GI disorders, systemic infections, increased ferritin and TSAT). GI AESIs reported in 2% or more subjects in either KRX-0502 or active control. GI AESIs reported with a higher frequency (>2% difference) in subjects receiving KRX-0502 vs. active control included diarrhoea (20.8% vs. 14.1%), discoloured faeces (19.7% vs. 0%), and constipation (7.5% vs. 5.4. GI AESIs reported with a higher frequency in subjects receiving active control compared with KRX-0502 included vomiting (14.8% vs. 6.8%), GI bleeding lower (2.7% vs. 0.2%), GI bleeding upper (4.0% vs. 1.3%), nausea (14.1% vs. 11.1%), and pancreatitis (2.0% vs. 0%). In subjects receiving KRX-0502, the frequency of subjects who experienced at least 1 GI AESI was highest during ≤4 weeks of exposure (38.4%); thereafter, the frequency declined over time, with 19.8% during >4 to 24 weeks. Across studies in the PSS, more subjects on active control experienced systemic infection AESI as compared to subjects on KRX-0502 (25.5% vs. 14.0%, respectively) and fewer on placebo (9.9%). The most frequently reported AEs in KRX-0502 treatment group were pneumonia/bronchitis (4.8%), graft/fistula infection, and Catheter/site infection (2% each), sepsis (1.6%), abscess (1.4%), and bacteraemia (1.1%). In PSS, the frequency of subjects who experienced at least 1 systemic infection AESI did not consistently increase with increasing exposure to KRX-0502. The frequency of AESIs increased with increasing KRX-0502 dose (<6, ≥ 6 to <9, and ≥ 9 g/day) for systemic infection AESIs (9.4%, 10.5%, and 37.5%, respectively). Administration of KRX-0502 leads to a significant increase in TSAT and ferritin levels, reaching a plateau at approximately 12 and 24 weeks. In Study 304, the permitted administration of IV iron as long as ferritin levels were <1000 ng/mL or TSAT levels were <30%, contributed to the increase in iron-related parameters: the percentage of subjects receiving IV iron was higher in KRX-0502 subjects who had maximum ferritin levels >1200 to ≤ 1500 ng/mL and >1500 ng/mL (90% and 83%, respectively) compared with lower maximum ferritin ≤ 1200 ng/mL (69%), and the cumulative IV iron dose was also highest in subjects who had a maximum ferritin >1500 ng/mL. The same pattern was observed with active control; among subjects in the 2 highest maximum ferritin categories, 100% received IV iron, compared with 83% in subjects with maximum ferritin ≤1200 ng/mL.

TEAEs and ADRs in non-dialysis population: The non-dialysis population showed somewhat numerically higher proportions of subjects, experiencing at least 1 TEAE as compared to placebo (~69% in 75 KRX received patients vs. ~59% in placebo patients). Similar trends observed in JTT formulation. Consistently higher ADR rates reported in KRX received non-dialysis patients as compared to placebo (~40% vs. ~18% for KRX and placebo, respectively). Similar trends observed also for JTT formulation. Consistently with dialysis population,

some features of time dependence was observed in non-dialysis population as it can be assessed based on JTT formulation for some AE categories (~70% vs. ~93% of TEAEs and ~32% vs. ~45% for ADRs, in case of <12 vs. >12 weeks duration of JTT use).

Serious adverse events and deaths

As of January 2015, a total of 36 deaths have been reported across the KRX-0502 development programme, representing an incidence of 1.5% (30/1947). None of the deaths was considered by the Investigator to be related to study drug. Of the subjects on KRX-0502, the most frequently occurring TEAEs associated with death were cardiac arrest (4 subjects [0.3%]), sudden death (3 subjects [0.2%]), and chest pain, pneumonia, sepsis and mental disorder (2 subjects [0.1%] each). Of the subjects receiving active control, cardiac arrest and endocarditis (2 subjects [0.1%] each) was the most frequently occurring TEAE associated with death; other PTs were reported in ≤1 subject death. In Study 304, the frequency of deaths during the 52-week SP was similar for subjects on KRX-0502 (13/289; 4.5%) and active control (8/149; 5.4%). In the long-term extension study 307, deaths were reported in 10/166 subjects (6.0%); 6 of the deaths were associated with cardiac disorders.

In the PSS, fewer KRX-0502-treated subjects reported SAEs (142/557, 26% [114/289, 39% in the 52-week SP of Study 304)]) compared with active control (73/149, 49%), and more compared with placebo (18/111, 16%). In KRX-0502 group (PSS), ≥5% subjects experienced SAEs within infections and infestations SOC and vascular disorders SOC. In the 52-week SP of Study 304, the most frequently reported SAE SOCs in the KRX-0502 group were infections and infestations, vascular disorders, surgical and medical procedures, general disorders and administration site conditions, which were all reported at a lower or comparable rate relative to the active control. In study 307, 75 of subjects (45.2%) experienced SAEs. The 5 most common SAEs were pneumonia, renal transplant, sepsis, fluid overload and pyrexia.

Incidence of SAEs in KRX-0502 subjects (PSS) increased with dose: 36/192 subjects (18.8%) in <6 g/day group, 77/285 (27.0%) in ≥6 to <9 g/day group, and 29/80 (36.3%) in ≥9 g/day group. Incidence of SAEs in KRX-0502 subjects (PSS) inconsistently increased with treatment duration: 35/557 subjects (6.3%) during ≤4 weeks, 65/420 (15.5%) during >4-24 weeks, 56/233 (24.0%) during >24-48 weeks, and 22/201 (10.9%) during >48 weeks exposure. In Study 304, fewer KRX-0502-treated subjects (100/289, 34.6%) experienced hospitalizations vs. the active control group (68/149, 45.6%) (relative difference: 24%; p=0.024).

Across the 3 non-dialysis studies, 18 of 70 subjects on KRX-0502/JTT-751 experienced 22 SAEs; 3 SAEs in 2 patients were considered to be possibly related to study drug. In placebo-controlled studies (Studies 204 and GBA4-4), the incidence of SAEs in subjects on KRX-0502/JTT-751 was comparable to placebo (Study 204: 8% vs. 12.3%, respectively; Study GBA4-4: 13.6% vs. 10%, respectively).

Thus, the total primary dialysis population showed somewhat lower proportion of subjects, experiencing at least 1 serious TEAE as compared to active control (~25% vs. 49% in pooled 557 KRX received PPS patients vs. 149 active control patients, respectively) and comparable mortality (2.5% vs. 5.4%, respectively). Somewhat different trends were observed in a direct comparison with active control with somewhat higher serious TEAE rates but lower mortality rates (39.3% vs. 30.9% but 4.5% vs. 5.4% in all 289 KRX received patients vs. 149 active control patients in Study 304, respectively). These rates were higher as compared to placebo (~16% and 0% in case of serious TEAEs and mortality rates). The lower serious ADRs rates reported in KRX received dialysis patients as compared to comparator (~1.1-1.4% vs. ~2.7% for KRX and Active comparator). Ne SADRS were observed in placebo group. Dose and time dependencies were observed for total, severe and serious TEAEs but not for ADRs. Time dependence is noted for SAEs (4.6% vs. 13.4%) in supportive studies.
A total of 30 deaths have been reported across the KRX development programme, representing an incidence of 1.5% (30/1947). None of the deaths was considered by the Investigator to be related to study drug.

Laboratory findings

The applicant presented studies 304 and 307, integrated laboratory findings for number of potentially clinically significant (PCS) values of for haematology (high haemoglobin, low Hb and Ht, ferritin > 1500 ng/mL, TSAT >50%, TSAT <30% and ferritin ≥800 ng/mL, phosphate <2.5 mg/dL, calcium <8.0 mg/dL, glucose >250 mg/dL, Abnormal AST, ALT or total bilirubin values) separately for dialysis and Non-dialysis populations. No specific findings signalling for worse safety of KRX were noted.

Safety in special populations

Subgroup analyses for AEs and SAEs were performed for the intrinsic (age, gender, race, body weight, diabetes status and baseline liver dysfunction) and extrinsic factors (in case of high increase in maximum ferritin, IV iron use and type of dialysis). For analysis, patients exposed to KRX-0502 and to active control in PSS were taken. No clinically significant or consistent trends signalling for worse safety of KRX could be noted but for the elderly where an increasing incidence in TEAE incidence was observed in the dialysis population and the non-dialysis population. Safety was not assessed for the long-term Therefore the SmPC informs the prescriber about limited data in the >75 year old. Also the applicant has committed to further investigate the safety profiling in the elderly and the impact of age groups >75 during post-marketing. A specific study investigating safety will be conducted and will include ~10% elderly form the planned 1000 patients.

Immunological events

No specific analysis on immunologic effects was performed.

Safety related to drug-drug interactions and other interactions

The subgroup analysis considering potentially interacting oral medications did not reveal any change in efficacy of KRX when taken with a number of frequently co-prescribed medications (fluoroquinolones, tetracyclines, proton pump inhibitors, thyroid hormones, sertraline, Vitamin D, warfarin, aspirin). The Applicant noted that, as KRX-0502 has a potential for drug-drug interactions which may affect the oral bioavailability of co-administered drugs, the drug should be administered approximately 2 hours before or after KRX, or the physician should consider monitoring suitable markers or clinical signs of efficacy, or blood levels of the concomitant medication if it has a narrow therapeutic window. SmPC states that KRX should not be administered with aluminium compounds because citrate is known to increase aluminium absorption.

Discontinuation due to adverse events

Potentially interacting oral medications: Subjects in the PSS were stratified by use of concomitant medications that could potentially be implicated in drug interactions with oral iron compounds. Eight drugs/categories of drugs (fluoroquinolones, tetracyclines, proton pump inhibitors, thyroid hormones, sertraline, Vitamin D, warfarin, aspirin), each with more than 10 subjects in the KRX-0502 group, were examined to determine AE profiles by SOCs, PTs and SAEs (see Table 18). Among the subjects on aspirin, proton pump inhibitors, thyroid hormones, vitamin D and warfarin, the proportion of subjects with at least 1 SAE was lower in the KRX-0502 group compared with that in the active control group (difference >10%). For the remaining drugs (fluoroquinolones, tetracyclines, sertraline), the incidence of SAEs was similar in both KRX-0502 and active control recipients. Despite the low number of subjects in the subgroups in the PSS hinders a robust analysis of TEAEs and concomitant medications, there was no pattern suggesting an increased incidence of TEAEs or SAEs among KRX-0502 treated subjects on these medications compared with active control. As the phosphate-binding activity of KRX-0502 relies on administration with food, this requirement is reflected in the product information. The Applicant noted that, as KRX-0502 has a potential for drug-drug interactions which may affect the oral bioavailability of co-administered drugs, medication should be administered approximately

2 hours before or after Fexeric, or the physician should consider monitoring suitable markers or clinical signs of efficacy or blood levels of the concomitant medication if it has a narrow therapeutic window. Furthermore, KRX-0502 should not be administered with aluminium compounds because citrate is known to increase aluminium absorption. Appropriate information has been included in the SmPC, section 4.5.

Table 18. AEs by selected concomitant medications

Category	Concomitant Medication	All KRX-0502 (N=557)	Active Control (N=149)	Placebo (N=111)
Subjects in the subgroup, n	Aspirin	294	82	66
	Bisphosphonates	3	1	1
	Fluoroquinolones	50	25	21
	Levodopa	7	1	2
	Methyldopa	0	0	0
	Penicillamine	0	0	0
	Proton pump inhibitor	176	72	38
	Sertraline	25	5	7
	Tetracyclines	13	3	7
	Thyroid hormone	29	6	4
	Valproate	1	0	1
	Vitamin D	393	137	86
	Warfarin	51	16	7
Subjects with at least 1 TEAE, n (%)	Aspirin	230 (78.2)	77 (93.9)	23 (34.8)
	Fluoroquinolones	47 (94.0)	24 (96.0)	8 (38.1)
	Proton pump inibitor	149 (84.7)	66 (91.7)	16 (42.1)
	Sertraline	21 (84.0)	4 (80.0)	3 (42.9)
	Thyroid hormone	27 (93.1)	5 (83.3)	1 (25.0)
	Tetracyclines	11 (84.6)	3 (100.0)	3 (42.9)
	Vitamin D	335 (85.2)	123 (89.8)	32 (37.2)
	Warfarin	40 (78.4)	15 (93.8)	2 (28.6)
Subjects with at least 1 SAE, n (%)	Aspirin	89 (30.3)	48 (58.5)	10 (15.2)
	Fluoroquinolones	33 (66.0)	17 (68.0)	6 (28.6)
	Proton pump inhibitor	71 (40.3)	42 (58.3)	8 (21.1)
	Sertraline	10 (40.0)	2 (40.0)	0
	Tetracyclines	9 (69.2)	2 (66.7)	1 (14.3)
	Thyroid hormone	12 (41.4)	4 (66.7)	0
	Vitamin D	118 (30.0)	67 (48.9)	16 (18.6)
	Warfarin	17 (33.3)	7 (43.8)	2 (28.6)

2.6.1. Discussion on clinical safety

Based on the data from 18 studies, the clinical trials included 1947 unique subjects with 1533 exposed to ferric citrate, 330 to active control and 262 to placebo. Among the 1533 subjects exposed to ferric citrate, there were 1388 subjects with CKD 5D and 145 subjects with CKD ND. Major part of this safety size is composed of KRX or very relevant to KRX formulation (JTT-751). Only minor part (68 patients) constitutes by non-specific (commercial) ferric citrate formulation. Overall, 659 subjects have received treatment with ferric citrate for ≥6 months, 378 for ≥1 year, and 29 subjects have completed 2 years (>96 weeks) of treatment. The majority of

subjects received titrated doses rather than fixed doses. The primary safety information comes from the PSS population for dialysis patients ((557 patients who received KRX, mainly from phase 3 study 304) and from main non-dialysis population (short term phase 2 Studies 204 and GBA4-4 and long-term Study GBA 4-7). The total primary dialysis population showed somewhat lower proportion of subjects, experiencing at least 1 TEAE as compared to active control (~77% vs. 89% in pooled 557 KRX received PPS patients vs. 149 active control patients). Although, the direct comparison with active control did show comparable TEAE rates (90.3% vs. 89.3% in all 289 KRX received patients vs. 149 active control patients in Study 304). In any case, this is higher as compared to placebo (39.6% in pooled 111 CKD HD patients from PPS population who received placebo).

Consistently higher ADR rates were reported in dialysis patients receiving KRX compared either comparator or placebo (~37% vs. ~12% vs. 3.6% for KRX, active comparator or placebo, respectively). These higher rates were driven mainly by GI ADRs (~34% vs. ~7% for KRX and active comparator, respectively). The applicant notes that the difference may be due to the exclusion of subjects with previous intolerance to the active control agents (sevelamer carbonate and/or calcium acetate) from Study 304. Across the 6 supportive dialysis studies TEAE rates were clearly lower compared to the PSS population but with clear feature of time dependence (for nasopharyngitis, diarrhoea and constipation, vomiting, excoriation, arthralgia and eczema).

Several key safety concerns were associated with phosphate binding agents and/or oral iron products (GI disorders, systemic infections, increased ferritin and TSAT). GI AESIs reported in 2% or more subjects in either KRX-0502 or active control. GI AESIs reported with a higher frequency (>2% difference) in subjects receiving KRX-0502 vs. active control included diarrhoea (20.8% vs. 14.1%), discoloured feces (19.7% vs. 0%), and constipation (7.5% vs. 5.4. GI AESIs reported with a higher frequency in subjects receiving active control compared with KRX-0502 included vomiting (14.8% vs. 6.8%), GI bleeding lower (2.7% vs. 0.2%), GI bleeding upper (4.0% vs. 1.3%), nausea (14.1% vs. 11.1%), and pancreatitis (2.0% vs. 0%). In subjects receiving KRX-0502, the frequency of subjects who experienced at least 1 GI AESI was highest during ≤4 weeks of exposure (38.4%); thereafter, the frequency declined over time, with 19.8% during >4 to 24 weeks. Appropriate statements were included into the product information and the detailed GI safety profiling analysing quantitatively the multiple adverse events frequencies during the long-term treatment will be further investigated during post-marketing in a dedicated PASS as described in the RMP.

Across studies in the PSS, more subjects on active control experienced systemic infection AESI as compared to subjects on KRX-0502 (25.5% vs. 14.0%, respectively) and fewer on placebo (9.9%). The most frequently reported AEs in KRX-0502 treatment group were pneumonia/bronchitis (4.8%), graft/fistula infection, and Catheter/site infection (2% each), sepsis (1.6%), abscess (1.4%), and bacteraemia (1.1%). In PSS, the frequency of subjects who experienced at least 1 systemic infection AESI did not consistently increase with increasing exposure to KRX-0502. The frequency of AESIs increased with increasing KRX-0502 dose (<6, ≥ 6 to <9, and ≥ 9 g/day) for systemic infection AESIs (9.4%, 10.5%, and 37.5%, respectively). The detailed infective safety profiling analysing quantitatively the multiple adverse events frequencies during the long-term treatment will be further investigated in a dedicated PASS during post-marketing as described in the RMP.

Administration of KRX-0502 leads to a significant increase in TSAT and ferritin levels, reaching a plateau at approximately 12 and 24 weeks, respectively. In the pivotal Study 304, the permitted administration of IV iron as long as ferritin levels were <1000 ng/mL or TSAT levels were <30%, contributed to the increase in iron-related parameters: the percentage of subjects receiving IV iron was higher in KRX-0502 subjects who had maximum ferritin levels >1200 to ≤ 1500 ng/mL and >1500 ng/mL (90% and 83%, respectively) compared with lower maximum ferritin ≤ 1200 ng/mL (69%), and the cumulative IV iron dose was also highest in subjects who had a maximum ferritin >1500 ng/mL. The same pattern was observed with active control; among subjects in the 2 highest maximum ferritin categories, 100% received IV iron, compared with 83% in subjects with

maximum ferritin ≤1200 ng/mL. The risk of iron overload induced by Fexeric administration is also subject of further evaluation within the PASS. Particularly, the concern on patients treated with high doses but with low metabolic demand of iron, such as men, patients on peritoneal dialysis, patients with high indices of iron stores either pre-treatment or during treatment is addressed by appropriate posology descriptions, a contraindication on iron overload syndromes and precaution statements on the monitoring of iron parameters. As per KDIGO guideline, the use of Fexeric should be temporarily discontinued if serum ferritin exceeds 800 ng/mL. This is also reflected in SmPC 4.2 and 4.4.

TEAEs and ADRs in non-dialysis population: The non-dialysis population showed somewhat numerically higher proportions of subjects, experiencing at least 1 TEAE as compared to placebo (~69% in 75 KRX received patients vs. ~59% in placebo patients). Similar trends observed in JTT formulation. Consistently higher ADR rates reported in KRX received non-dialysis patients as compared to placebo (~40% vs. ~18% for KRX and placebo, respectively). Similar trends observed also for JTT formulation. Consistently with dialysis population, some features of time dependence was observed in non-dialysis population as it can be assessed based on JTT formulation for some AE categories (~70% vs. ~93% of TEAEs and ~32% vs. ~45% for ADRs, in case of <12 vs. >12 weeks duration of JTT use). For this purpose, the Applicant committed to perform a post-marketing surveillance plan in the EU for long-term data in non-dialysis patients. Furthermore the SmPC section 4.2 reports that long term safety data are limited in non-dialysed patients.

The total primary dialysis population showed somewhat lower proportion of subjects, experiencing at least 1 serious TEAE as compared to active control (~25% vs. 49% in pooled 557 KRX received PPS patients vs. 149 active control patients, respectively) and comparable mortality (2.5% vs. 5.4%, respectively). Some what different trends were observed in a direct comparison with active control with somewhat higher serious TEAE rates but lower mortality rates (39.3% vs. 30.9% but 4.5% vs. 5.4% in all 289 KRX received patients vs. 149 active control patients in Study 304, respectively). These rates were higher as compared to placebo (~16% and 0% in case of serious TEAEs and mortality rates). The lower serious ADRs rates reported in KRX received dialysis patients as compared to comparator (~1.1-1.4% vs. ~2.7% for KRX and Active comparator). No SADRS were observed in placebo group. Dose and time dependencies were observed for total, severe and serious TEAEs but not for ADRs. Time dependence is noted for SAEs (4.6% vs. 13.4%) in supportive studies. A total of 30 deaths have been reported across the KRX development programme, representing an incidence of 1.5% (30/1947). None of the deaths was considered by the Investigator to be related to study drug.

The applicant presented studies 304 and 307 and integrated laboratory findings for number of potentially clinically significant (PCS) values of for haematology (high haemoglobin, low Hb and Ht, ferritin > 1500 ng/mL, TSAT >50%, TSAT <30% and ferritin ≥800 ng/mL, phosphate <2.5 mg/dL, calcium <8.0 mg/dL, glucose >250 mg/dL, Abnormal AST, ALT or total bilirubin values) separately for dialysis and Non-dialysis populations.

Safety in special populations: Subgroup analyses for AEs and SAEs were performed for the intrinsic (age, gender, race, body weight, diabetes status and baseline liver dysfunction) and extrinsic factors (in case of high increase in maximum ferritin, IV iron use and type of dialysis). For analysis, patients exposed to KRX-0502 and to active control in PSS were taken. No clinically significant or consistent trends signalling for worse safety of KRX could be noted but for the elderly where an increasing incidence in TEAE incidence was observed in the dialysis population and the non-dialysis population was not assessed for the long-term Therefore, the SmPC informs the prescriber about limited data in the >75 year old. The CHMP requested to applicant to further investigate the safety profiling in the elderly and the impact on patients in age groups >75 years in the post-marketing setting. A PASS including ~10% elderly form the planned 1000 patients was agreed.

The subgroup analysis considering potentially interacting oral medications did not reveal any change in efficacy of KRX when taken with a number of frequently co-prescribed medications (fluoroquinolones, tetracyclines,

proton pump inhibitors, thyroid hormones, sertraline, Vitamin D, warfarin, aspirin). However KRX-0502 has a potential for drug-drug interactions which may affect the oral bioavailability of co-administered drugs (such as ciprofloxacin and levothyroxine). From in vitro studies, antibiotic (doxycycline, cefdinir), anticonvulsant (valproate sodium), antidepressant (sertraline HCl), bisphosphonate (alendronate sodium), anti-parkinsonian (levodopa) and immunosuppressant (methotrexate) medications showed the potential to interact with Fexeric. Therefore the SmPC recommends that any of these or other medicinal products that have the potential to interact with Fexeric, should be taken at least 2 hours before or after Fexeric.

Furthermore the physician should consider monitoring suitable markers or clinical signs of efficacy, or blood levels of the concomitant medication if it has a narrow therapeutic window as described in the SmPC.

The percentage of subjects who experienced at least 1 TEAE that led to discontinuation of study drug was slightly higher for subjects receiving KRX-0502 than for those receiving active control or placebo (12.0% [14.2% in Study 304] vs. 9.4% or 2.7%, respectively). The dominating SOCs TEAE leading to discontinuation in the KRX group overall were GI disorders (6.8%; diarrhoea 3.6%) and surgical and medical procedures SOC (2.2%; all of them were renal transplant). In contrast, dominant SOC in the active control group was not a GI but surgical and medical procedures (4.7%) and metabolism and nutrition disorders SOC.

Administration of KRX-0502 leads to a significant increase in TSAT and ferritin levels, reaching a plateau at approximately 12 and 24 weeks. To take due account of this important potential risk the SmPC has introduced a warning in section 4.4 in SmPC that increases in ferritin and transferrin saturation (TSAT) are observed with Fexeric use. Fexeric should be used only in the absence of iron overload syndromes and with caution if serum ferritin rises above 500 ng/mL. Fexeric should be temporarily discontinued if serum ferritin exceeds 800 ng/mL. Significantly elevated ferritin levels were observed particularly when concomitant intravenous iron was used. Long term safety concerns in CKD patients will be further elucidated post-authorisation by the means of a non-interventional PASS as described in the RMP and Annex II as it is considered key to the benefit risk balance. The Final report is to be submitted 31 December 2020.

2.6.2. Conclusions on the clinical safety

The CHMP considers the clinical safety of Fexeric acceptable to conclude on a positive risk benefit evaluation. The applicant agreed to conduct several studies investigating the safety profile of Fexeric, especially the occurrence of infections and gastrointestinal adverse effects. Long term safety will also be studied. Furthermore, the CHMP considered the conduct of the following dedicated PASS as key to the benefit risk and necessary to address issues related to safety in the elderly and in patients potentially over-loaded with iron:

Non-interventional post-authorisation safety study (PASS): prospective, observational, multicentre, 2-arm parallel study in CKD patients treated with Fexeric in comparison to patients treated with iron-free phosphate-binders in order to gain long-term (2 years) safety data (including iron overload events with subgroups analysis for serum ferritin levels above 500 ng/mL and 800 ng/mL, infective and gastrointestinal events) particularly in EU patients, elderly and very elderly patients, dialysed (hemodialysis (HD) and peritoneal dialysis (PD)) and non-dialysed patients.

This study is categorised as 1 and is imposed as a condition to the marketing authorisation (Annex II). The Final report is to be submitted 31 December 2020.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 could be acceptable if the applicant implemented the changes to the RMP as described in the PRAC advice and PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes requested by the PRAC. The advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 24 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal inflammation, bleeding and erosion • Hyperaluminaemia due to interaction of aluminium-containing drugs and citrates • Hypophosphataemia • Reduction in the therapeutic effect of co-administered ciprofloxacin
Important potential risks	• Iron accumulation • Hepatoxicity • Potential for harm from overdose in children • Reduction in the therapeutic effect of co-administered doxycycline, cefdinir, valproate sodium, sertraline HCl, alendronate sodium, levodopa, methotrexate and thyroxine
Missing information	• Safety in pregnant and breast feeding women • Effects on fertility • Safety in children, including potential off-label use • Use in elderly (≥75 years old) • Long term safety in CKD ND and PD patients

Pharmacovigilance plan

Table 25: Ongoing and planned studies in the PhV development plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
KRX-0502-401 (non-interventional, 1)	To evaluate the long term safety of KRX-0502 when used in normal clinical practice. To confirm safety in long-term administration in post-authorisation for up to 2 years in HD, PD and CKD ND patients and in patients ≥75 years old	Gastrointestinal AEs inflammation, bleeding and erosion Hypophosphataemia Iron accumulation / hepatotoxicity, Risk of hyperaluminiumaemia in patients receiving KRX-0502 concomitantly with aluminium-containing medicinal product, Use in elderly (≥75 years old), Long term safety in CKD ND and PD patients	Planned	Final report to be submitted by 31 December 2020.
RIO-PMS-JT-001 (non-interventional, 3)	To confirm safety (in particular iron accumulation) in long-term administration in post-marketing for one year or more in HD, PD and CKD ND patients	Gastrointestinal AEs inflammation, bleeding and erosion Hypophosphataemia Iron accumulation / hepatotoxicity Use in elderly (over 75 years old) Long term safety in CKD ND and PD patients	Planned	Final report: Q4 2021
KRX-0502-JTOX-003 (non-clinical, 3)	To assess the toxicity of orally administered ferric citrate in juvenile rats	Safety in children	Planned start: June 2015	Final report: March 2016

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, (including the synopsis for the Non-Interventional Observational Post-authorisation Study to Assess the Safety of Fexeric in Normal Clinical Practice, which has been assessed in detail in the appended assessment report) was of the opinion that the applicant should submit a full protocol for the study 'A Non-Interventional Observational Post-authorisation Study to Assess the Safety of Fexeric in Normal Clinical Practice' within 3 months of approval with consideration to the issues outlined on pages 74-84 in the a m report .

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table 26 of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Gastrointestinal inflammation, bleeding and erosion	Proposed text in SmPC Contraindication in Section 4.3: Active severe gastrointestinal disorders (eg, gastrointestinal bleeding) Warning in Section 4.4: Patients with active, symptomatic inflammatory bowel disease were excluded from clinical trials. Fexeric should only be used in these patients following careful assessment of benefit/risk. Listed in section 4.8: *Adverse reactions observed during clinical studies in which Fexeric was administered in CKD Stage 5 patients on haemodialysis or peritoneal dialysis* *Uncommon (≥1/1000, <1/100)*: gastritis, gastritis erosive, haematemesis, peptic ulcer *Adverse reactions observed during clinical studies in which Fexeric was administered in non-dialysis-dependent patients with CKD Stages 3-5.* *Common (≥1/100, <1/10)*: haematochezia	None
Hyperaluminaemia due to interaction of aluminium-containing drugs and citrates	Proposed text in SmPC Section 4.5 Interaction Since citrate is known to increase aluminium absorption, aluminium-based compounds should be avoided while patients receive Fexeric.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypophosphataemia	Proposed text in SmPC Section 4.2 Posology and method of administration *Dose titration* Serum phosphorus concentrations should be monitored within 2 to 4 weeks of starting or changing the dose of Fexeric, and approximately every 2-3 months when stable. The dose of Fexeric can be increased or decreased by 1 to 2 g (1 to 2 tablets) per day at 2- to 4-week intervals as needed to maintain serum phosphorus at recommended target levels, up to a maximum dose of 12 g (12 tablets) per day. There are limited data available for doses higher than 9 g (9 tablets) per day in CKD patients not on dialysis; therefore in this population doses higher than 9 g/day should be used with caution. Temporarily discontinue Fexeric if the serum phosphorus is < 3 mg/dl and resume at a lower dose once the serum phosphorus has returned to the target range. Section 4.3 Contraindications: Hypophosphataemia Listed in section 4.8: *Adverse reactions observed during clinical studies in which Fexeric was administered in CKD Stage 5 patients on haemodialysis or peritoneal dialysis* *Metabolism and nutrition disorders* *Uncommon (≥1/1000, <1/100)*: hypophosphataemia Adverse reactions *observed during clinical studies in which Fexeric was administered in non-dialysis-dependent patients with CKD Stages 3-5.* *Metabolism and nutrition disorders* *Common (≥1/100, <1/10)*: hypophosphataemia	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Reduction in the therapeutic effect of co-administered ciprofloxacin	Proposed text in SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction *Effects of Fexeric on other medicinal products* In drug-drug interaction studies in healthy male and female subjects, Fexeric decreased the bioavailability of concomitantly administered ciprofloxacin (as measured by the area under the curve [AUC]) by approximately 45%. However, there was no interaction when Fexeric and ciprofloxacin were taken 2 hours apart. Consequently, ciprofloxacin should not be taken at the same time, but at least 2 hours before or after Fexeric.	None
Iron accumulation / hepatotoxicity	Proposed text in SmPC Section 4.2 Posology *Starting dose* CKD patients who are not on dialysis require the lower starting dose, 3 g (3 tablets) per day. *Dose titration* There are limited data available for doses higher than 9 g (9 tablets) per day in CKD patients not on dialysis; therefore in this population doses higher than 9 g/day should be used with caution. Treatment with Fexeric may lead to elevations in iron stores, particularly in patients receiving concomitant intravenous iron therapy. Fexeric should be temporarily discontinued if serum ferritin exceeds 800 ng/ml (see section 4.4). Long-term safety data are limited in non-dialysis and peritoneal dialysis patients (see section 5.1) *Hepatic impairment* Experience from clinical studies in patients with hepatic impairment is limited. No dosage reduction is considered necessary but patients with hepatic impairment should initiate treatment with the lower starting dose, 3 g (3 tablets) per day (see section 5.1). Section 4.3 Contraindications: Haemochromatosis or laboratory tests indicating possible haemochromatosis	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other iron overload (primary or secondary) syndromes Warning in Section 4.4: Monitoring iron parameters Increases in ferritin and transferrin saturation (TSAT) are observed with Fexeric use. Fexeric should be used only in the absence of iron overload syndromes and with caution if serum ferritin rises above 500 ng/ml. Fexeric should be temporarily discontinued if serum ferritin exceeds 800 ng/ml. Significantly elevated ferritin levels were observed particularly when concomitant intravenous iron was used. All patients receiving this medicine require at least quarterly monitoring of serum iron storage parameters (serum ferritin and TSAT). Serum ferritin and TSAT levels increase after intravenous iron administration; hence, blood samples for measurement of iron storage parameters should be obtained at a time appropriate to reflect the patient's iron status after intravenous iron dosing taking into account the product used, the amount of iron given and the frequency of dosing, but a minimum of 7 days after intravenous iron dosing. Patients treated with Fexeric should not receive concomitant treatment with other oral iron preparations. Reductions in intravenous iron and erythropoiesis-stimulating agent (ESA) use with this medicine have been observed. Therefore, patients may need reduction in, or discontinuation of, intravenous iron and/or ESAs.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential for harm from overdose in children	Proposed text in SmPC: Section 4.9 (Overdose): Iron overdose is dangerous, particularly in children, and requires immediate attention. The symptoms of acute iron overdose include vomiting, diarrhoea, abdominal pain, irritability, and drowsiness. If someone is known or suspected to have accidentally or intentionally ingested an overdose of Fexeric, immediate medical attention should be sought.	None
Safety in children, including potential off-label use	Proposed text in SmPC: Section 4.2 Posology and method of administration: The safety and efficacy of Fexeric in children and adolescents aged 0 to 18 years has not yet been established. No data are available	None
Reduction in the therapeutic effect of co-administered drug interaction with doxycycline, cefdinir, valproate sodium, sertraline HCl, alendronate sodium, levodopa, methotrexate and thyroxine	Proposed text in SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction *Effects of Fexeric on other medicinal products* From in vitro studies, certain antibiotic (doxycycline, cefdinir), anticonvulsant (valproate sodium), antidepressant (sertraline HCl), bisphosphonate (alendronate sodium), anti-parkinsonian (levodopa) and immunosuppressant (methotrexate) medications showed the potential to interact with Fexeric: any of these or other medicinal products that have the potential to interact with Fexeric should be taken at least 2 hours before or after Fexeric. Since iron-based preparations are known to reduce the absorption of levothyroxine (thyroxine), physicians should consider monitoring suitable markers or clinical signs of efficacy if these medicinal products are concomitantly administered with Fexeric. Although the potential for interactions with medicinal products seems low, for concomitant treatment with products with a narrow therapeutic window, the clinical effect/adverse events should be monitored, on initiation or dose adjustment of Fexeric or the concomitant product.	None
Safety in pregnant and breast feeding women	Proposed text in SmPC: Section 4.6 Fertility, pregnancy and lactation: Pregnancy There are no data regarding the use of ferric	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	citrate coordination complex in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Fexeric is not recommended during pregnancy and in women of childbearing potential not using contraceptive methods. Breast-feeding It is not known whether ferric citrate coordination complex/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fexeric therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.	
Effects on fertility	Proposed text in SmPC: Section 4.6 Fertility, pregnancy and lactation: No data are available on the potential influence of Fexeric on fertility.	None
Use in elderly (over 75 years old)	Proposed text in SmPC Section 4.2: *Elderly population* Experience from clinical studies in patients above the age of 75 years is limited.	None
Long term safety in CKD ND and PD patients	Proposed text in SmPC Section 4.2 Posology and method of administration: Long term safety data are limited in non-dialysis and peritoneal dialysis (PD) patients (see section 5.1)	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice with changes. These changes concerned the following elements of the Risk Management Plan - Conduct of the PASS as a category 1 study imposed as a condition to the marketing authorisation:

KRX-0502-401 - Non-interventional post-authorisation safety study (PASS): prospective, observational, multicentre, 2-arm parallel study in CKD patients treated with Fexeric in comparison to patients treated with iron-free phosphate-binders in order to gain long-term (2 years) safety data (including iron overload events with subgroups analysis for serum ferritin levels above 500 ng/mL and 800 ng/mL, infective and gastrointestinal events) particularly in EU patients, elderly and very elderly patients, dialysed (haemodialysis (HD) and

peritoneal dialysis (PD)) and non-dialysed patients. The CHMP justified these changes as follows: The PASS is considered key to the benefit risk balance and therefore is Category 1 as described in the RMP and Annex II. The Final report is to be submitted 31 December 2020.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Fexeric (Ferric citrate coordination complex) is included in the additional monitoring list as it considered a new active substance as well as there is a PASS.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the overall clinical programme conducted with Fexeric, this medicinal product showed sP lowering effect in both dialysis and non-dialysis CKD population. The results of the main efficacy studies demonstrate that KRX-0502, taken in divided doses during meals at starting doses of 3 to 6 g/day and titrated based on serum Pi levels up to a maximum of 12 g/day, is effective for the control of hyperphosphataemia in adult CKD patients both Stage 5 undergoing HD and PD or in CKD-ND.

- Dialysis population: In the pivotal study for this population KRX-0502 maintained sP_i from week 52 to week 56 (placebo controlled phase), as it is shown by mean change of ~ –0.24 mg/dL in via several analyses, whereas the sP_i increased in the placebo group (mean change of ~ 1.4 to 1.8 mg/dL, leading to absolute effect (the difference over placebo) of ~−2.18 mg/dL. The responder rate (as assessed by achievement of sPi ≤ 5.5 mg/dL) was 71.4% as compared to 20.9% for placebo.

The sP relative effect was comparable to active controls at week 12 (mean KRX lowering effect from baseline was −2.02 mg/dL) vs. −2.22 mg/dL (all active controls) and vs. −2.21 mg/dL(sevelamer as a single agent). Similarly, the responder rate also comparable (62.3% and 63.0% for KRX-0502 and active control, respectively).

- Non-dialysis population. The levels of sP constantly decreased more (by ~–0.5 mg/dL) for the studied population in KRX as compared to placebo group (~-0.7 vs. ~-0.2).

The effect was consistent through several sensitivity analyses and the efficacy result in subgroups were broadly consistent.

Uncertainty in the knowledge about the beneficial effects

Although in the clinical development programme Fexeric demonstrated positive effects on control of hyperphosphataemia in adult patients with chronic kidney disease, its long-term safety in CKD patients, the dialysed (hemodialysis (HD) and peritoneal dialysis (PD)) and non-dialysed population (due to the risk of iron overload), and in the elderly remain be further investigated in a post-authorisation setting. A non-interventional PASS as described in the RMP and Annex II was imposed by the CHMP as it is considered key to the benefit-risk evaluation.

Risks

Unfavourable effects

Oral phosphate binders bind phosphate in the gastrointestinal tract, either by forming an insoluble complex or by binding it into a resin and hence, the gastrointestinal effects are attributed to their mechanism of action. Consistently higher ADR rates reported in KRX received dialysis patients as compared either comparator or placebo (~37% vs. ~12% vs. 3.6% for KRX, active comparator or placebo, respectively). These higher rates are driven mainly by GI ADRs (~34% vs. ~7% for KRX and active comparator, respectively). Gastrointestinal AESIs were reported in 2% or more subjects in either KRX-0502 or active control. Those reported with a higher frequency (>2% difference) in subjects receiving KRX-0502 vs. active control included diarrhoea (20.8% vs. 14.1%), discoloured faeces (19.7% vs. 0%), and constipation (7.5% vs. 5.4. GI AESIs reported with a higher frequency in subjects receiving active control compared with KRX-0502 included vomiting (14.8% vs. 6.8%), GI bleeding lower (2.7% vs. 0.2%), GI bleeding upper (4.0% vs. 1.3%), nausea (14.1% vs. 11.1%), and pancreatitis (2.0% vs. 0%).In subjects receiving KRX-0502, the frequency of subjects who experienced at least 1 GI AESI was highest during ≤4 weeks of exposure (38.4%); thereafter, the frequency declined over time, with 19.8% during >4 to 24 weeks. The most commonly reported adverse reactions in non-dialysis dependent CKD (CKD ND) subjects during treatment were discolored faeces, constipation and diarrhoea occurring in 27%, 13% and 11% of patients. Gastrointestinal inflammation, bleeding and erosion were therefore defined as an important identified risk in the RMP and appropriate statements are made in the product information.

Administration of KRX-0502 leads to a significant increase in TSAT and ferritin levels, reaching a plateau at approximately 12 and 24 weeks, respectively. The risk of iron overload induced by Fexeric administration (with particular focus on patients treated with high doses but with low metabolic demand of iron, such as men, patients on peritoneal dialysis, patients with high indices of iron stores either pre-treatment or during treatment) was taken into account into the SmPC adapting the posology in patients who do not require dialysis and contraindications in haemochromatosis and in patients with iron overload syndromes. Furthermore, precautionary statements were added advising on the monitoring of iron parameters.

KRX-0502 has a potential for drug-drug interactions which may affect the oral bioavailability of co-administered drugs (such as ciprofloxacin and levothyroxine). From in vitro studies, antibiotic (doxycycline, cefdinir),

anticonvulsant (valproate sodium), antidepressant (sertraline HCl), bisphosphonate (alendronate sodium), anti-parkinsonian (levodopa) and immunosuppressant (methotrexate) medications showed the potential to interact with Fexeric. Therefore, the SmPC recommends that any of these or other medicinal products that have the potential to interact with Fexeric, should be taken at least 2 hours before or after Fexeric.

Uncertainty in the knowledge about the unfavourable effects

The proportions of elderly dialysis patients with at least one serious adverse reaction were 0.7% for ages <65 years (3/451), 1.4% for ages 65-<75 years (1/73), and 6.0% for ages ≥75 years (2/33)]. While the proportion of affected patients increased with age, this trend was not statistically significant; the 95% CI for patients aged ≥75 years is 6.0 ± 8.1% and therefore includes the proportions of patients with related SAEs for ages <65 years and for ages 65-<75 years. The product information takes this into account and informs about the limited experience in patients over 75 years. Nevertheless, the number of elderly patients over 75 years old were low in the clinical development program, and the use of Fexeric in over 75 years old is considered as missing information in the Risk Management Plan. Detailed safety profile in the elderly (age ≥ 75 years) will be evaluated postmarketing via a postauthorisation safety study in order to evaluate the safety of Fexeric in ~1000 patients in the EU.

The risk of iron overload induced by Fexeric administration is also subject of further evaluation within the PASS. As already stated above of particular concern are patients treated with high doses but with low metabolic demand of iron, such as men, patients on peritoneal dialysis, patients with high indices of iron stores either pre-treatment or during treatment. This is sufficiently addressed for marketing authorisation by appropriate posology descriptions, a contraindication on iron overload syndromes and precaution statements on the monitoring of iron parameters. As per KDIGO guideline, the use of Fexeric should be temporarily discontinued if serum ferritin exceeds 800 ng/mL as reflected in SmPC 4.2 and 4.4.

Long term safety concerns in CKD patients mainly, the dialysed (hemodialysis (HD) and peritoneal dialysis (PD)) and non-dialysed population (due to the risk of iron overload) and the elderly and will be further elucidated post authorisation by the means of a non-interventional PASS as described in the RMP and Annex II as it is considered key to the benefit risk balance.

Benefit-risk balance

Importance of favourable and unfavourable effects

Chronic kidney disease (CKD) is a major health burden in the EU. In Europe, the overall unadjusted prevalence of patients receiving HD or PD, a proxy measure for ESRD, was 531 pmp at end 2010. i.e. an overall population of approximately 270 000 patients in the EU. Once GFR decreases to below ~25 ml/min/1.73 m2 (CKD Stage 4-5), compensatory mechanisms are insufficient to balance the dietary intake, resulting in hyperphosphataemia. The resulting disruption in mineral homeostasis leads to a clinical syndrome – CKD-mineral and bone disease (CKD-MBD) – characterised by bone and musculoskeletal abnormalities as well as extraskeletal (vascular and soft tissue) calcification implicated in cardiovascular morbidity and mortality.

The results of the main efficacy studies demonstrate that KRX-0502, taken in divided doses during meals at starting doses of 3 to 6 g/day and titrated based on serum Pi levels up to a maximum of 12 g/day, is effective for the control of hyperphosphataemia in adult CKD patients both Stage 5 undergoing HD and PD or in CKD-ND. This makes the treatment effect particularly valuable for the dialysis population. The unfavourable effects remain broadly comparable to active comparators except GI ADRs and the long-term safety in non-dialysis population (primarily regarding the non-dialysis EU population, elderly (>75 years) and multiple ADRs

(predominantly GI and infection) and due to the risk of iron overload will need to be further substantiated by post-authorisation studies to ascertain the long term safety profile.

Benefit-risk balance

Discussion on the benefit-risk balance

Throughout the clinical investigations of Fexeric in the control of hyperphosphataemia in adult patients with chronic kidney disease, sufficient clinical and therapeutic benefit has been shown. All observed risks can be considered balanced with implemented risk minimisation measures either in the product information or in the RMP. Long term safety concerns in CKD patients mainly, the dialysed (hemodialysis (HD) and peritoneal dialysis (PD)) and non-dialysed population (due to the risk of iron overload), and in the elderly will be further elucidated post-authorisation, by means of a non-interventional PASS as described in the RMP and Annex II. This study is considered key to the benefit risk balance characterisation.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Fexeric indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): prospective, observational, multicentre, 2-arm parallel study in CKD patients treated with Fexeric in comparison to patients treated with iron-free phosphate-binders in order to gain long-term (2 years) safety data (including iron overload events with subgroups analysis for serum ferritin levels above 500 ng/mL and 800 ng/mL, infective and gastrointestinal events) particularly in EU patients, elderly and very elderly patients, dialysed (hemodialysis (HD) and peritoneal dialysis (PD)) and non-dialysed patients.	Final report to be submitted by 31 December 2020.

New Active Substance Status

Based on the CHMP review of data on the non-clinical and clinical properties of the active substance, the CHMP considers that Ferric Citrate Coordination Complex which is a complex is qualified as a new active substance as it differs significantly in properties with regard to safety and efficacy from the previously authorised substance.