27 March 2025
EMA/130313/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xoanacyl

International non-proprietary name: ferric citrate coordination complex

Procedure No. EMEA/H/C/006402/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ACR	Albumin to creatinine ratio
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
CI	Confidence interval
CKD	Chronic kidney disease
CKD 5HD	Chronic kidney disease stage 5 with haemodialysis
CKD 5PD	Chronic kidney disease stage 5 with peritoneal dialysis
CKD-MBD	Chronic kidney disease-mineral and bone disease
CO_2	Carbon dioxide
CSR	Clinical study report
DBPC	Double-blind placebo-controlled
DD	Dialysis-dependent
DDI	Drug-drug interaction
DP	Drug product
DS	Drug substance
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
ESA	Erythropoiesis-stimulating agent
ESRD	End stage renal disease
EU	European Union
FCCC	Ferric citrate coordination complex
FDA	Food and Drug Administration
FGF23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
GI	Gastrointestinal
HD	Haemodialysis
HDPE	High density polyethylene
Hgb	Haemoglobin
hr	Hour
HRQoL	Health-related quality of life
HyperP	Hyperphosphataemia
iFGF23	Intact fibroblast growth factor 23
ICH	International Conference on Harmonisation
IDA	Iron deficiency anaemia
ISS	Integrated summary of safety
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KDQOL	Kidney Disease and Quality of Life Instrument
KRX-0502	FCCC, i.e., AVA1014, Xoanacyl
LS	Least squares

LOCF	Last observation carried forward
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measure
NA	Not applicable
ND	Not done
NDD	Non-dialysis-dependent
OL(E)	Open label (extension)
P	Phosphate
PBRER	Periodic benefit risk evaluation report
PCS	Potentially clinically significant
PD	Peritoneal dialysis
PK	Pharmacokinetic
PP	Per protocol
PPI	Proton pump inhibitor
PT	Preferred term
PTH	Parathyroid hormone
RCT	Randomised clinical trial
S-P	Serum phosphate
SAP	Statistical analysis plan
SAEs	Serious adverse events
SD	Standard deviation
SE	Standard error
SF-12	12-item short form health survey [SF 12]
SOC	System organ class
TEAEs	Treatment-emergent adverse events
TIBC	Total iron binding capacity
TID	Three times a day
TSAT	Transferrin saturation
UIBC	Unsaturated iron-binding capacity
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Averoa submitted on 5 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Xoanacyl, 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 20 July 2023.

The applicant applied for the following indication:

Xoanacyl is indicated for the treatment of iron deficiency anaemia in adult chronic kidney disease (CKD) patients with elevated serum phosphorus levels.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision P/0036/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0036/2024 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Applicant's request for consideration

1.5.1. 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 ferric citrate coordination complex previously authorised in the European Union as Fexeric, as the applicant claimed that Ferric citrate coordination complex differs significantly in newly demonstrated properties with

regard to safety and/or efficacy from the already authorised active substance.

1.6. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	5 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	17 June 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	26 June 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	27 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	03 January 2025
The PRAC agreed on the PRAC assessment overview and Advice to CHMP during the meeting on	16 January 2025
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	30 January 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	21 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	23 January 2025
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 Xoanacyl on	27 March 2025
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product (see	27 March 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for Xoanacyl in the EU is: *Treatment of iron deficiency anaemia (IDA) in adult CKD patients with elevated serum phosphorus.*

Chronic kidney disease (CKD) is a structural or functional abnormality of the kidneys that has health implications and been present for more than 3 months. The aetiology of CKD may remain unknown or be attributed to another systemic disease and/or a localised condition within the kidney. CKD is often progressive.

Besides the obvious effects on excretion of waste products and superfluous fluids, there is a multitude of secondary problems arising with progressing CKD, such as hyperphosphataemia, secondary hyperparathyroidism, hyperkalaemia, iron deficiency, anaemia, hypertension, and metabolic acidosis. In the longer run, subjects with CKD have increased risk of cardiovascular diseases and mineral-bone disorders (CKD-MBD).

2.1.2. Epidemiology

CKD is a progressive condition that affects >10% of the general population worldwide, amounting to >800 million individuals (Kovesdy, 2022).

The prevalence of anaemia associated with CKD in European adults was reported to range from 12.8% to 61.5% (Mathias et al., 2020), with increasing prevalence in those > 60 years of age and more advanced CKD. Earlier reported epidemiologic and bone marrow biopsy studies have estimated the prevalence of iron deficiency in Non-dialysis dependent (NDD)-CKD patients to be 48% to 98% (Fishbane et al., 2009; Gotloib et al., 2006; Stancu et al., 2010). Similarly, anaemia in dialysis dependent (DD) CKD patients is frequent, with a published international study on anaemia management highlighting that approximately 53% of patients had Hgb < 10g/dL 30 days after haemodialysis (HD) start (Karaboyas et al., 2020).

Hyperphosphataemia is a prevalent comorbidity of CKD, affecting 50–74% of patients with renal disorders (Leaf and Wolf, 2013).

2.1.3. Aetiology and pathogenesis

Iron deficiency anaemia (IDA) in CKD

Iron deficiency is broadly categorised as absolute (total body iron deficit with reduced levels of both circulating and stored iron) or functional (reduced circulating iron that limits erythropoiesis despite normal or elevated iron stores). The risk of IDA can occur at any stage of CKD but increases with increasing kidney impairment. IDA would be present by default if left untreated in patients on dialysis.

The cause of the iron deficiency and IDA in patients with CKD is multifactorial and includes reduced erythropoietin (EPO) production, increased levels of hepcidin, use of erythropoiesis stimulation agents (ESAs) that can cause an iron demand exceeding its supply, reduced dietary intake, increased blood loss (particularly in patients undergoing haemodialysis), poor bone marrow responsiveness or suppression, and shortened red blood cell survival (Babitt et al., 2021). Hepcidin, expressed in the

liver, becomes elevated (as a consequence of inflammation, decreased renal clearance, and reduced EPO production; Babitt et al., 2021). This decreases iron availability as it inhibits the absorption of iron from the GI tract as well as its release from iron stores in the body.

Hyperphosphataemia in CKD

Phosphate is normally excreted renally. Hyperphosphataemia in CKD is caused by accumulation of alimentary phosphate exceeding the excretion via the impaired kidneys.

2.1.4. Clinical presentation, diagnosis

Iron deficiency anaemia

Iron deficiency and modest anaemia is often asymptomatic. With worsening anaemia, symptoms like fatigue and weakness develop. More pronounced anaemia may lead to more serious complications, such as hypotension, or coronary and pulmonary insufficiency. This is more common in older individuals with underlying pulmonary and cardiovascular disease.

The gold standard for the diagnosis of iron deficiency is measurement of iron stores in bone marrow obtained on biopsy. However, this is rarely done in CKD patients in clinical practice. Instead, iron stores are more commonly estimated by measurement of serum iron, total iron-binding capacity (TIBC), ferritin, and calculation of the percent transferrin saturation (TSAT).

Definitions and recommendations for treatment targets in iron deficiency in subjects with CKD are discussed in the KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease (Kidney international Suppl Vol 2, Issue 4, 2012).

A very low serum ferritin (≤30 ng/ml) is indicative of iron deficiency. The 2012 KDIGO guideline states that "except in this circumstance, the TSAT and serum ferritin level have only limited sensitivity and specificity in patients with CKD for prediction of bone marrow iron stores and erythropoietic response to iron supplementation. Their utility is further compromised by substantial inter-patient variability unrelated to changes in iron store status. Evidence to support a recommendation for specific TSAT and ferritin levels at which iron therapy should be initiated or as 'targets' for iron therapy is limited, with very few RCTs." The 2012 KDIGO guideline further states that "Most CKD patients with serum ferritin levels ≥100 ng/ml have normal bone marrow iron stores, yet many such patients will also have an increase in Hb concentration and/or reduction in ESA dose if supplemental iron is provided. Therefore, for patients who have not been receiving iron supplementation, we suggest iron administration in anaemic CKD patients with TSAT ≤30% and serum ferritin ≤500 ng/mL if an increase in Hb level is desired, particularly if intended to avoid transfusions and reduce anaemia-related symptoms, and/or reduction in ESA dose, after consideration of the potential risks of iron administration."

More recent data from the PIVOTAL study supported the safe and effective use of a high dose of intravenous (IV) iron in the DD population with ferritin concentration up to >700 ng/mL or the transferrin saturation was ≥40% (Macdougall et al., 2019).

Taken together, there are currently no fixed target levels for TSAT and ferritin during iron supplementation; however, it is often recommended to discontinue iron treatment at ferritin ≥ 800 ng/mL to mitigate the risks of iron overload.

A low haemoglobin (Hgb) concentration and/or low haematocrit are the parameters most widely used to diagnose anaemia. The cut-off level for Hgb varies between sources, but Hgb <13 g/dL for males and <12 g/dL for females is commonly regarded as anaemia.

Hyperphosphataemia

Hyperphosphataemia is usually asymptomatic. Regular monitoring of serum phosphate is typically used for the diagnosis.

2.1.5. Management

The clinical management of CKD patients with iron deficiency and elevated phosphorus is individualised based on the clinical status of the patient and level of kidney impairment and currently requires each aspect to be managed by different therapies.

Iron deficiency anaemia

Iron supplementation is widely used in CKD patients to treat iron deficiency, prevent its development in erythropoiesis stimulating agent (ESA) treated patients, raise Hb levels in the presence or absence of ESA treatment, and reduce ESA doses in patients receiving ESA treatment.

Currently used oral iron products are simple iron salts such as iron sulphate, iron gluconate, or iron fumarate. Among the adverse reactions with oral iron products is a well-known high rate of GI side effects contributing to poor adherence to therapy. Furthermore, the efficacy of oral iron supply in the DD-population is often low. An alternative is the administration of IV iron, which is more frequently used in patients receiving dialysis where it can be co-administered during dialysis.

According to the 2012 KDIGO anaemia guideline, a clearly defined advantage or preference for IV compared to oral iron was not supported by available evidence in CKD NDD patients. Therefore, in such patients, the route of iron administration can be either IV or oral. In some patients, particularly those with mild iron deficiency, the desire to avoid venipuncture and preserve IV access may favour an initial trial of oral iron. There is however evidence supporting a preference for the IV route of iron administration in CKD 5HD patients derived from RCTs and other studies comparing IV iron with currently available oral iron formulations and placebo, with and without concomitant ESA treatment. In most of these studies, IV iron administration led to a greater increase in Hb concentration, a lower ESA dose, or both. In CKD 5HD patients, the ready IV access and convenience of being able to administer IV iron during HD treatments further supports the preference for the IV route for iron administration in these patients.

As untreated iron deficiency is an important cause of the lack of responsiveness to ESA therapy, iron supplementation is required in the majority of patients receiving dialysis to ensure adequate iron supply for erythropoiesis and to minimise the dose of ESA required (NICE Clinical Guidelines on Anaemia Management in CKD, 2011; McFarlane et al., 2010).

Hyperphosphataemia

In the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update (M Ketteler et al., 2017), the Work Group abandoned the previous suggestion to maintain phosphate in the normal range, instead suggesting that treatment be focused on patients with hyperphosphataemia. Particularly in the case of CKD patients not on dialysis, the 2017 Update Work Group clarified that phosphate-lowering therapies may only be indicated in the event of "progressive or persistent hyperphosphatemia," and not to prevent hyperphosphataemia.

A variety of phosphate-binding agents have been used clinically. These include aluminium salts, calcium salts, sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate.
The use of aluminium salts is very uncommon nowadays due to the systemic absorption of aluminium which may result in dementia, encephalopathy, microcytic anaemia, and osteomalacia. Calcium salts are inexpensive, but the use is limited in higher doses due to the risk of hypercalcaemia and an

increased [calcium x phosphate]-product. In the 2017 KDIGO CKD-MBD guideline update, restricting the dose of calcium-based phosphate binders in adult patients with CKD G3a–G5D was recommended. Calcium-free phosphate binders, such as sevelamer and lanthanum, are expensive and with side effects such as gastrointestinal distress and binding of essential nutrients. Still, they are recommended over calcium-based phosphate binders in the 2017 KDIGO updated guideline.

Velphoro is another iron-based phosphate binder centrally approved in the EU. The active substance in Velphoro is sucroferric oxyhydroxide. Velphoro is indicated for the control of serum phosphorus levels in adult CKD patients on HD or peritoneal dialysis (PD) and in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate). In the KDIGO 2017 CKD-MBD guideline, it is stated that the Work Group discussed iron-containing phosphate binders but decided that these did not affect the recommendations given the absence of data on long-term patient-centred outcomes at that time point.

In summary, there are other available treatments for iron deficiency (oral iron, parenteral iron) and hyperphosphataemia (calcium-based phosphate binders, calcium-free phosphate binders) all with their specific advantages and disadvantages. There is however no other product on the EU-market intended for use in subjects with both iron deficiency and elevated serum phosphorous.

2.2. About the product

In the EU, a 1g film-coated tablet product containing FCCC was previously authorised under the legal basis of Article 8(3) of Directive 2001/83/EC via the centralised procedure. The brand name was Fexeric, with the approved indication "for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD)". The product was first approved on 23 September 2015 by Keryx Biopharma UK Ltd (transferred to Akebia Europe Ltd, a subsidiary of Akebia Therapeutics Inc). However, Fexeric was never launched, and the Marketing Authorisation Application (MAA) fell under the sunset clause and was officially withdrawn in June 2020. No product containing FCCC is currently authorised for use in the EU.

Averoa SAS has licensed from Akebia Therapeutics, Inc, the rights to develop the FCCC product in Europe, and Averoa has the right of reference to all FCCC/KRX-0502/JTT-751 studies. The originally proposed indication was "*for the treatment of iron deficiency anaemia in adult chronic kidney disease (CKD) patients with elevated serum phosphorus levels*".

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as film coated tablets containing 1 g of ferric citrate (as coordination complex, containing 210 mg of ferric iron).

Other ingredients are:

Tablet core: pregelatinised starch, calcium stearate*;*

Film coating: hypromellose, titanium dioxide (E171), triacetin, sunset yellow FCF (E110), allura red AC (E129) and indigo carmine (E132).

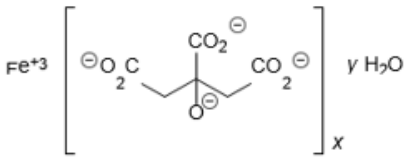
The product is available in high density polyethylene (HDPE) bottles sealed with child-resistant polypropylene screw caps, an aluminium foil heat-sealed with a polyethylene liner and two silica gel sachets, as described in section 6.5 of the SmPC.

2.3.2. Active Substance

2.3.2.1. General information

The chemical name of the active substance is Iron (+3), x (1, 2, 3-Propanetricarboxylic acid, 2-hydroxy-), y (H2O), corresponding to the molecular formula Fe • x(C6H4O7) • yH2O; x=0.70-0.87, y=1.9–3.3 and it has the structure shown in Figure 1. The relative molecular weight of the anhydrous formula $FeC_6H_5O_7$ is 244.94.

Figure 1: active substance structure



Ferric citrate coordination complex (FCCC) has a unique chemical structure consisting of a di-anionic compound, namely a dinuclear di-ferric-di-citrate complex, ($[Fe_2Cit_2(H_2O)_2]^{2-}$), and a cationic complex, ferric hexaaquairon ($[Fe(H_2O)_6]^{3+}$). The dinuclear complex consists of predominantly 2:2 (ferric iron: citrate).

The formula for FCCC is $[Fe(H_2O)_6]_2[Fe_2Cit_2(H_2O)_2]_3$ and thus the molar ratio of citrate to ferric is approximately 6/8 or 0.75:1. The weight ratio of citrate to ferric iron in Ferric Citrate Coordination Complex is approximately 60%:20% of active substance (on an as-is basis).

The structure of is derived from its route of synthesis and is confirmed by spectral (UV, IR, 1H- and 13C- NMR, and Mossbauer spectroscopy) analyses. Physical characterisation has been performed by polarised light microscopy, scanning electron microscopy, melting point-hot stage microscopy, thermogravimetric analysis, differential scanning calorimetry, hygroscopicity measurement, X-Ray powder diffraction, PSD and BET.

The active substance (AS) is light brown to beige amorphous, slightly hygroscopic powder with occasional dark specks. It is freely soluble in water (>200 mg/mL) is the physicochemical characteristics have been presented and discussed. It shows no polymorphism and has no chiral centres.

2.3.2.2. Manufacture, characterisation and process controls

The active substance manufacturer has been stated. Satisfactory documentation regarding the GMP status of the site and the relevant QP declarations have been provided during the procedure resolving a MO raised by CHMP in this regard.

The commercial manufacturing process for FCCC active substance utilises two starting materials and involves two reaction steps. Initially a MO was raised about the choice of one of the two starting materials. The applicant in their response further justified the choice of the starting material (SM); the response was considered scientifically sound and thus the SM is acceptable. The AS manufacturing process has been described in sufficient detail. A reworking step is described. Typical overall yields for the entire process and typical batch size have been clearly stated. The manufacturing process has been validated at the proposed site in accordance with GMP requirements.

Critical steps and corresponding CPPs have been satisfactorily presented. Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials and

reagents have been presented and are acceptable. The proposed holding-times are supported by data and are acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The manufacturing process development has been described in sufficient detail.

The active substance is packaged in double polyethylene bags inside a fibre drum with a secure fitting lid. Two desiccants are placed between the two bags.

The polyethylene bags comply with the EU Commission regulation No 202/2014 relating to plastic materials and articles intended to come into contact with foodstuffs, and its subsequent amendments.

2.3.2.3. Specification

The active substance specification includes tests for: appearance, identification of ferric (Ph. Eur.), identification of citrates (Ph. Eur.), identification of FCCC (IR), assay for ferric ion (titrimetric), citrate content (HPLC), assay for ferric ion/citrate content weight ratio, related substances (HPLC), ferrous ion content (titrimetric), chloride content (titrimetric), residual organic solvent (GC), water content (KF), acid insolubles (gravimetric), elemental impurities (ICP-MS), particle size distribution (Ph. Eur.), BET surface area (Ph. Eur.), specific synthesis impurity (X-ray powder diffraction) and microbial limits (Ph. Eur.).

The proposed specification methods and limits are acceptable. The proposed specifications are based on a statistical analysis performed on a large number of historical batches and batches manufactured at the commercial batch size by the proposed manufacturer with the commercial process manufactured with the commercial process.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the used reference standards testing has been presented.

The batch analysis data from six representative batches (including three validation batches) produced at the proposed manufacturer were presented. All the batches were manufactured according to the commercial manufacturing process and were analysed according to the analytical methods described in Section 3.2.S.4.2. All batches meet the specifications.

2.3.2.4. Stability

Stability data from seven commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25ºC / 60% RH), 12 months under intermediate conditions (30ºC / 65% RH), and for 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The stability samples were evaluated against acceptance criteria in place at the time of testing for appearance, ferric iron and citrate assay, degradation products, ferrous iron content, water content, acid insolubles and microbial quality. Changes to the analytical procedures and acceptance criteria in place during the stability study were presented in Section 3.2.S.7.3.

All the stability results at long-term 25°C/60%RH, intermediate 30°C/65%RH and accelerated 40°C/75%RH conditions, remained within specifications during the reporting period.

Photostability testing following the ICH guideline Q1B was performed on one batch. The sample was analysed for appearance, ferric content, citrate content, related impurities and water content. The results showed that the AS is sensitive to light but the container closure system protects it from light.

During development, samples of Ferric Citrate Coordination Complex active substance were subjected to forced degradation conditions. The forced degradation study confirmed the suitability of the assay and purity methods to separate and quantify Ferric Citrate Coordination Complex and potential degradation products and confirms that the methods are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container and protected from light.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product (FP), also referred to as AVA1014, is presented as film-coated, peach-coloured and oval-shaped tablets debossed with "KX52". The tablet size is approximately 19 mm long, 7.2 mm thick and 10 mm wide.

The composition of FCCC tablets containing 1 g FCCC (equivalent to 210 mg ferric iron) per tablet, including the quality standard and function of each component, as well as the composition of the film coating has been provided in the dossier.

The related certificates of analysis have been provided. All other excipients in the FP are compendial 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.

The compatibility of ferric citrate coordination complex with the tablet core excipients was evaluated. No evidence was found for incompatibility of Ferric Citrate Coordination Complex with the excipients of the tablet core.

The pharmaceutical development has been designed to keep the dosage form as small as possible, using the least possible amounts of excipients, due to high specific surface area of the AS which is needed for pharmacological activity. A quality target product profile (QTPP) has been presented.

The AS quality attributes that can potentially affect FP performance, were studied to meet the target FP profile.

The medicinal product is intended only for adult patients and therefore, no paediatric issues are present. The dimension of the capsule appears appropriate for the intended population. It is noted that the posology of AVA1014 considers up to a maximum of 12 g (12 tablets) per day. This is a high number of tablets for the patient, however it should be noted that the main phosphate binders on the European market have similar posology and therefore patients are used to taking a high number of tablets. Moreover, it is acknowledged that the pharmaceutical development has been designed to keep the dosage form as small as possible, using the less possible quantity of excipients, due to high specific surface area of the AS which is needed for pharmaceutical activity.

Several formulation studies were carried out to develop a commercial, high loading dosage form with a suitable composition for processing that maintained appropriate quality attributes. A conventional

granulation manufacturing process is used to produce the FP. Initial development studies were carried out by a development site, scale up studies were performed by another manufacturer and then by the proposed FP manufacturing site.

The product from the proposed FP manufacturing site has not been used in clinical setting. Clinical studies have been performed using batches produced by the development site. Bridging of the to-be-marketed product to the product used in the clinical studies was based on in vitro data. A history of batches used in clinical trials and stability studies has been provided in the dossier. No bioequivalence studies were necessary.

In order to demonstrate the comparability of the batches produced by the two manufacturers, the applicant submitted comparative in vitro data of the validation batches at the proposed FP manufacturing site and of validation batches performed at scale up site and of representative batches from the development site. In addition to the reported in vitro data, the applicant discussed the observed difference of batches produced the proposed FP manufacturing site as compared to the development site has a from a efficacy and safety point of view; this is accepted.

The applicant also adequately discussed minor manufacturing and composition quantitative changes, concluding that the quality of the FP manufactured in the development site and the proposed commercial FP manufacturing site is considered comparable and thus the bridging between the to-be-marketed product to the product used in the clinical studies is considered demonstrated.

The FCCC is amorphous and exhibits a high specific surface area, which is primarily due to its high porosity. FCCC is highly soluble (>200 mg/ml in water at 37°C) in water. The solubility of the FCCC at physiological conditions of the human gastrointestinal (GI) tract corresponds to the "highly soluble" category of the Biopharmaceutical Classification System (BCS) Guidance. Citrate is complexed and chelated with ferric iron via covalent bonds, thus masking iron from water and inhibiting the formation of polynuclear hydroxide complexes, hence, maintaining ferric iron in solution at the GI conditions.

The development of dissolution method was adequately presented and the discriminatory power of the dissolution method has been better demonstrated.

The primary packaging is high density polyethylene (HDPE) bottles sealed with child-resistant polypropylene screw caps, an aluminium foil heat-sealed with a polyethylene liner and two silica gel sachets (desiccant). The HDPE material complies with Ph. Eur. and EC requirements. The specifications for desiccant sachet were provided. The desiccant bags comply with EC regulation (EU) no 10/2011 on plastic materials and articles intended to come into contact with food.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The FP manufacturing site and other sites involved in the secondary packaging batch release and testing have been stated in the dossier. The manufacturers are properly authorised for the intended manufacturing phases. Each manufacturer has an adequate GMP certification. An updated QP declaration, based on audit performed within past three years has been presented resolving an MO raised in this respect.

The manufacturing process consists of six main steps: screening, granulation, drying lubrication/blending, compression, coating and packaging. The manufacturing process is a standard process and utilises conventional manufacturing techniques and equipment.

The theoretical batch size for commercial manufacture of FCCC 1 g tablets was stated and the detail of batch formula has been provided.

Critical steps were defined and the respective process controls for all critical steps are put in place. In-process controls performed during FP packaging step have also been specified along with the acceptance criteria and analytical methods used.

The proposed maximum storage of the bulk product is supported by stability data**.** Information on primary bulk product packaging has been provided and is considered adequate. Compliance with the Note for Guidance on start of shelf-life of the finished dosage form (CPMP/QWP/072/96) has been confirmed.

The FP manufacturing process has been validated using three consecutive full-scale batches. The final product was evaluated according to, and met, the specifications. Thus, the process validation of the FP manufacturing process was successfully completed and no concerns are raised.

2.3.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including appearance, identification of citrate (colorimetric), identification of FCCC (IR), identification of ferric salt (colorimetric), 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.).

Generally, the proposed acceptance criteria are in line with the results of batch analysis or with stability findings. The selected methods for the analysis of the medicinal product are adequate considering the formulation.

The acceptance criteria of the dissolution method have been sufficiently discussed. The proposed impurity limits are in accordance with ICH Q3B and ICH Q3C(R8), taking into account the maximum daily dose for the active substance i.e. 12 g, this is acceptable based on the provided batch and stability results.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The stability indicating nature of the HPLC method used for testing of the assay and related substances has been studied by stress testing in photo and thermal degradation conditions, and acidic, basic oxidative conditions. The microbiological method has been

verified and this method is suitable for use in testing proposed FP. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results were provided for five commercial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The information related to the batch size, site of manufacture, date of manufacture, AS batch numbers have been indicated. All the test results remain within the specification limits.

2.3.3.4. Stability of the product

Stability data from five commercial scale batches of finished product stored for up to 24 months under long term conditions (25°C / 60% RH), for up to 12 under intermediate conditions (30°C / 65% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The stability batches of are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The stability samples were evaluated for appearance, assays (ferric iron, citrate and ferrous iron), impurities, dissolution, water content and microbiological tests. The analytical procedures used are stability indicating.

No significant change occurs for any of the tested attribute at either long term and intermediate conditions, however significant changes occur for one specification parameter at the accelerated condition after 3 months. Out of specification results at the accelerated condition have been previously observed and are considered a known trend. Nevertheless, since no extrapolation beyond the period covered by long-term data is proposed, the proposed shelf life can be accepted.

Supportive stability data from another three commercial scale batches manufactured by the scale up site stored in all three above stability conditions were also provided covering up to 36 months under long term conditions have been also presented further supporting the proposed shelf life.

In addition, one representative batch of bulk film coated tablets was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that exposure to light does not significantly affect the properties of the FP.

In-use stability study was conducted on one batch of FP packaged in the commercial packaging. The results of the in-use stability study confirmed that the FP in the proposed packaging is stable 2 months after first opening as stated in SmPC sections 6.3 and 6.4. The duration of the 2 months in-use shelf life is consistent with the average treatment duration.

Based on available stability data, the proposed shelf-life of 2 years and storage conditions as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.3.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Two Majors Objection were raised during the procedure concerning the update of the QP declaration and the justification of the starting material for the AS synthesis. Both were resolved by the provision of updated documentation and additional information by the applicant. The results of tests carried out indicate 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.

2.3.5. 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.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Pharmacological and pharmacokinetic effects of Xoanacyl are derived from submitted bibliographic publications. The toxicological programme included seven repeat dose toxicology studies conducted in rats and in dogs and four juvenile toxicity studies in rats. All other studies of the toxicological programme relied on the existing scientific literature.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The applicant claims that due to the well-known properties of ferric, ferrous and citrate compounds, the pharmacological strategy of FCCC was based on literature data, in compliance with ICH M3(R2) guideline. In addition, GLP toxicity studies were used to obtain safety pharmacology information.

The primary pharmacological effects of FCCC, i.e. increasing iron blood parameters and lowering serum and urine phosphate levels are supported by *in vitro* and *in vivo* pharmacodynamic literature studies in healthy and in mouse and rat models of CDK. Furthermore, statistically significant increases in iron serum levels and decreases in urinary phosphorus excretion have been observed in the toxicity studies conducted in rats and dogs. *In vitro* published data show that FCCC has certain affinity for phosphate over the acidic pH range, but in the neutral pH environment bounding this capacity is diminished. Furthermore, in a published study (Iida *et al*., 2013), FCCC was shown to be able to bind 46 ± 2 mg phosphorus/g product at pH 2-7.

From *in vivo* published data, effects of KRX-0502 and of ferric citrate have been studied in healthy rats as well as in mouse and rat models of CDK. FCCC (3% w/w in diet) has been shown to have no effect on iron biochemical parameters when administered during 2 weeks to normal Sprague Dawley rats (Hsu *et al*., 1999). The same study reflects that urinary phosphate excretion was drastically reduced corresponding to decreased phosphorus absorption from the GI tract and lower serum phosphorus levels. FCCC (0.3 to 3% w/w in diet) has been also shown to reduce phosphorus absorption and increase phosphorus faecal excretion following 7 days of treatment in normal rats (Iida *et a*l., 2013). In CKD rodent models, different authors have demonstrated that animals treated with FCCC had

increased iron absorption, increasing serum iron and haematocrit and decreased the intestinal absorption of phosphate, lowering the serum phosphate concentrations.

The applicant claims that the ability to increase iron blood parameters and the high capacity to bind phosphorous of FCCC, the active substance of Xoanacyl, is likely related to its larger specific surface area.

2.4.2.2. Secondary pharmacodynamic studies

The applicant has provided several literature references on possible secondary pharmacodynamics effects of FCCC that may improve some comorbidities of the CDK, such as ectopic aorta calcification, hyperparathyroidism and bone abnormalities. Also, chronic metabolic acidosis occurs commonly during renal impairment and the citrate absorbed following treatment with FCCC has the capacity to reduce acidosis and to prevent the associated loss of bone mass. Moreover, the FCCC treatment has shown decreases in markers of systemic and kidney inflammation, improved kidney function, and decreased kidney fibrosis, displaying a renoprotective effect in CKD patients, in particular, Ferric citrate coordination complex has a dual mechanism of action, one that is associated with providing a source of ferric iron and one associated with decreasing the absorption of phosphorous. The dual mechanism of action result in a direct impact on reducing functionally active intact fibroblast growth factor 23 (iFGF-23). Stimulation of FGF23, as a compensatory mechanism, is linked to poor cardiovascular outcome in CKD.

2.4.2.3. Safety pharmacology programme

No dedicated safety pharmacology core battery study has been performed with FCCC on the basis of the known toxicity profile of iron and citrate and the lack of meaningful systemic exposure following a single dose. Safety endpoints were evaluated through assessments performed during the repeat-dose toxicity studies. In addition, literature references documenting the effects of the ferric and of the ferrous ion were also supplied.

From the presented documentation no safety pharmacology effects have been identified except on the colour and consistence of stools and occasional trembling, stereotypies, circling, favouring limb, salivation, lacrimation, and ocular redness 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, meningeal haemorrhage, congestion, oedema and degenerated cortical neurons in animals treated and altered behaviour and long-term memory with the iron fortified diet.

A published study carried out in SD male rats administered with iron-supplemented diets containing 350-20000 µg Fe/g of food for 12 weeks, reveals that the heart/body ratio was increased in this species and cardiomyopathy, myocardial degeneration and necrosis were also observed (Whittaker *et al*., 1996). In several clinical studies, no direct effects of iron on the ECG and blood pressure have been identified and a correlation between iron load and QTc has not been clearly established. It should be highlighted that citrate transiently decreased the QTc when administered IV, although this finding was not observed following oral administration.

No safety pharmacology effects of oral iron and citrate formulations on the respiratory system were identified from the scientific literature.

2.4.2.4. Pharmacodynamic drug interactions

The complexing properties of iron suggest that FCCC 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 are discussed in pharmacokinetic drug interactions section.

2.4.3. Pharmacokinetics

The nonclinical pharmacokinetic package submitted for this procedure relied on bridging toxicokinetic data on the systemic exposure to the iron moiety of ferric citrate following oral administration, available from the assessments of blood iron parameters (serum iron, transferrin saturation [TSAT, ferritin and total iron binding capacity [TIBC) which were included in six toxicology studies (three studies in rats [two GLP studies], three in dogs [two GLP studies]). Information on the absorption of the citrate moiety and on the distribution, metabolism and excretion of ferric citrate is documented using references to the scientific literature. A number of *in vitro* drug interaction studies have been conducted to evaluate the potential of ferric citrate to bind to drugs which are concomitantly administered and to determine if they form insoluble precipitates.

2.4.3.1. Analytical methods

Serum iron concentration, ferritin concentration, TIBC and TSAT were evaluated using standard validated methods as part of the preclinical assessment of the toxicity studies in rats and dogs.

2.4.3.2. Absorption

Measurements of iron parameters (serum or plasma iron, ferritin, TIBC and TSAT) were included in six of the seven repeat dose toxicity studies in rats and dogs to address toxicokinetics requirements. Standard pharmacokinetic profile in plasma with FCCC (i.e. C*max*, AUC, $t_{1/2}$) was not assessed due to its main GI effect and the resulting small fraction of iron in plasma.

In this regard, studies in rats and dogs showed that iron from FCCC was not significantly absorbed after oral administration for up to 28 days. In longer studies, the 90-day (13 weeks) and 32-week in rats, and the 16-week and 42-week in dogs, serum iron and other iron parameters, as well as histopathological evaluations, indicated a dose- and time-dependent absorption of iron.

In male rats, after 13 weeks of dosing at 2800 mg/kg/day, there were statistically significant increases in serum iron, ferritin, and TSAT and decreases in TIBC. In female rats, ferritin was statistically significantly higher than controls after 13 weeks of dosing at ≥1400 mg/kg/day and serum iron was lower than controls after 13 weeks of dosing at 2800 mg/kg/day. TSAT was increased only after 32 weeks of treatment at 2800 mg/kg/day. In the 13-week study, female TIBC was significantly lower than controls at the end of dosing at 2800 mg/kg/day but was significantly higher than controls at 2800 mg/kg/day at the end of the recovery period in the 32-week study. Four weeks after the cessation of dosing in this study, female ferritin levels were statistically significantly higher than controls at ≥1400 mg/kg/day.

In dogs, no changes in iron parameters were observed at doses up to 500 mg/kg/day for 16 weeks, or doses up to 400 mg/kg/day for 42 weeks, with the exceptions of a slight but statistically significant increase in ferritin in female dogs at 400 mg/kg/day after 42 weeks of dosing, and small decreases in serum iron at 16 weeks at 400 mg/kg/day in the 42-week study and at 500 mg/kg/day in the 16-week study.

In the 42-week study, following 16 weeks administration of a dose level of 2000 mg/kg/day, ferritin values were statistically significantly higher than controls in both sexes. At the dose level of 2800 mg/kg/day in the 16-week study, serum iron was statistically significantly higher than controls in both sexes and the differences in ferritin relative to controls were markedly greater than at lower doses (and 9- to 15-times higher than in controls). TIBC was generally lower than controls at doses ≥1000 mg/kg/day in both studies, but the differences were observed to be statistically significant only in the males at weeks 16 and 42. Serum iron and TSAT were lower than controls in both sexes at dose levels lower than 2800 mg/kg/day. After 42 weeks serum iron and TSAT were significantly higher than controls in males and females at 2000 mg/kg/day. Ferritin continued to increase in males at ≥1000 mg/kg/day and in females at 400 mg/kg/day and above. TIBC levels were significantly lower in males at doses ≥1000 mg/kg/day.

After the 30-day recovery period in the 16-week study, ferritin at 1200 and 2800 mg/kg/day in both sexes and serum iron in both sexes at 2800 mg/kg/day were still higher than controls. However, TIBC was similar to control values in the males. In the 42-week study, ferritin was statistically significantly higher than controls at the end of the recovery period in both the males and females in the 2000 mg/kg/day group.

A comparison of ferritin levels achieved with the highest doses of ferric citrate in long-term toxicological studies in rats and dogs and patients treated for 1 year with 6 g/day FCCC (pivotal phase III study) showed that serum ferritin levels were similarly increased in rats treated for 32 weeks with 2800 mg/kg than in patients for 52 weeks, while dogs administered 2000 mg/kg for 42 weeks reached an exposure to iron 2.5 times higher than serum ferritin level of humans at 6 g/day.

2.4.3.3. Distribution

Following repeated-dose treatment with ferric citrate in rats, iron deposition, evaluated microscopically as a pigment deposited in the tissues of several animals affected, was observed in the small and large intestine (in tissue macrophages) as well as in liver, spleen, kidney and lymph nodes (≥500 mg/kg at 13 and 32 weeks) and, to a lesser extent, in ovaries, pancreas and lungs. In dogs, a similar pattern was observed, with the small and large intestine, liver, spleen and lymph nodes being the main organs of iron deposition. Pigment deposition was occasionally observed in kidneys, heart and pancreas, and was also observed in bone marrow at ≥1000 mg/kg/day at week 42.

As for a placental transfer study published in the literature, when ferrous citrate is administered to pregnant rats, only 72% of foetal iron is derived from maternal liver iron stores, suggesting that up to 28% may come from sources other than maternal non-haem iron, such as absorption during pregnancy and maternal haem metabolism.

In another published study which examined the citric acid content of groups of tissues in a single male mouse, it was observed that acid citric was present in bone, whereas soft tissues did not contain significant reserves of citrate.

2.4.3.4. Metabolism

No metabolism studies were performed for FCCC since metabolism of iron and citrate is well established.

2.4.3.5. Excretion

No excretion studies were conducted with ferric citrate in animal species since mammals have no physiologic process for iron excretion. Results from several published studies were submitted to document the excretion of iron and citrate.

The complex iron-phosphorous formed at gastrointestinal level is excreted in stool. In addition, 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. Iron loss also occurs in patients following haemodialysis.

For citrate, results from scientific literature show that approximately 55% of the administered dose in rats was present in expired CO_2; whereas 27% to 34% of the dose was recovered in the urine.

2.4.3.6. Pharmacokinetic drug interactions

Three *in vitro* studies were conducted to evaluate the potential for FCCC to inhibit the absorption of 48 concomitantly administered drugs via formation of an insoluble precipitate in simulated human gastric fluid or different parts of the gastrointestinal tract. Additional experiments were conducted to evaluate quantitatively the effect of incubating FCCC with the ten compounds that had visible precipitates in the earlier experiments. Finally, two additional *in vitro* drug-drug interaction (DDI) studies were conducted assessing the time-course interaction of 16 drugs representative of the therapeutic classes of drugs usually used in CKD patients.

Based on the all the submitted studies, a total of 12 medications showed at least one positive *in vitro* test. These were alendronate sodium, benserazide HCl, cefdinir, ciprofloxacin HCl, digoxin, doxycycline hyclate, levodopa, levofloxacin HCl, methotrexate, sertraline HCl, valproate sodium, and vancomycin HCl. With the exception of digoxin, a DDI was not observed in the clinical study in healthy volunteers.

In addition, the applicant has submitted four published studies performed in rats which describe reduced absorption of methyldopa and levodopa (L-3,4-dihydroxyphenylalanine, or L-dopa) due to formation of ferric iron complexes in the intestine, the potential for phenobarbital to increase absorption of intragastrically administered iron in rats, and inhibition of phenytoin anticonvulsant activity by dietary iron feeding in mice.

Finally, the *in vivo* DDI studies conducted in healthy volunteers for ciprofloxacin, digoxin, glimepiride, losartan, diltiazem and clopidogrel showed a direct DDI with FCCC only for ciprofloxacin.

2.4.3.7. Other pharmacokinetic studies

2.4.3.7.1. Toxicokinetic in juvenile toxicology studies

Nonclinical data related to the absorption of iron from FCCC were included in two non-GLP juvenile toxicity studies in rats to address toxicokinetics requirements, where standard iron parameters (serum or plasma iron, ferritin concentration, TIBC, and TSAT) were evaluated.

Changes in iron parameters were observed following 1 week, 2 weeks or 56 days of dosing with FCCC at the 2800 mg/kg/day dose at PND21 to 76. These changes included increases in serum iron levels, ferritin, and TSAT and decreases in TIBC and UIBC.

2.4.4. Toxicology

The toxicological programme included three studies in Sprague-Dawley rats (28-day [4-week], 90-day [13-week], and 32-week durations) and four studies in beagle dogs (28-day [4-week], 33-day, 16-week and 42-week durations) as well as four juvenile toxicity studies in Sprague-Dawley rats. Information pertaining to single-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity studies can be found in the published literature.

2.4.4.1. Single dose toxicity

No single dose toxicity studies have been conducted with FCCC nor have data been identified in the published literature for FCCC. However, studies evaluating the acute toxicity following oral administration of other iron- and citrate-containing compounds, the two components in FCCC, are described in the scientific literature. According to this published literature, animals exposed to lethal doses of iron compounds have shown decreased activity, weakness, decreased muscular control, prostration, urination, bowel obstruction, gastroenteritis (including diarrhoea 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 haemorrhagic necrosis of the gastrointestinal tract (GIT). Lethal doses of citric acid 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.

2.4.4.2. Repeat dose toxicity

2.4.4.2.1. Repeat dose toxicity in Rats

Three studies have been conducted with FCCC administered in the diet in the Sprague-Dawley rat: a 28-day dose range finding study and a 90-day and a 32-week toxicity study.

No product related deaths have been reported. Change in iron parameters indicative of increased iron absorption were observed at 2800 mg/kg dose level in both males and females, in studies longer than 28 days. Increases in serum phosphorus (at doses ≥2000 mg/kg administered for 28 days and ≥500 mg/kg administered for 90 days or more) and decreases in urinary phosphorus excretion were also observed (at doses ≥2000 mg/kg administered for 28 days and ≥500 mg/kg administered for 13 weeks or more) in all studies. Reversible decreases were observed in PTH levels in males (2800 mg/kg). There was a small, but significant decrease in serum calcium in females at doses >1400 mg/kg when ferric citrate was administered for at least 90 days, and in males at 3500 mg/kg in the 28-day study.

Macroscopic and microscopic findings of black material throughout the GIT were observed; this was considered to be unabsorbed test article. Pigmented macrophages were present in the stomach, intestine, and colon, and iron granules were present in epithelial cells. Other microscopic findings in the small and large intestine included increased mixed inflammatory cell infiltrates, increased number and/or size of goblet cells/goblet cell hyperplasia, mucosal/submucosal thickening, and basophilia in rats receiving doses ≥1400 mg/kg (302 mg Fe/kg/day). Colonic goblet cell hyperplasia and/or increased size of the colonic glands were also noted in male rats at doses ≥500 mg/kg and muscularis externa thickening of the colon was observed in females at doses ≥1000/1400 mg/kg for 32 weeks. These GI histopathology findings were reversible with the exception of the presence of pigmented macrophages.

The incidence and severity of brown pigment in the Kupffer cells in the liver, macrophages in the spleen, and tubular epithelial cells in the kidneys were dose-dependently increased in the ferric citrate-treated animals following 90 days and 32-weeks of dosing. This finding was evident at doses ≥1000/1400 mg/kg in the liver and kidney and at doses ≥500 mg/kg in the spleen. Iron deposits in the liver, spleen, and kidneys did not change appreciably during the recovery periods.

2.4.4.2.2. Repeat dose toxicity in dogs

The applicant submitted four repeated-dose toxicity studies of FCCC in the Beagle dog: a 28-day dose range finding study which included a dosing formulation feasibility/ palatability test, a 33-day, two-phase, maximum tolerated dose study, a 16-week toxicity study and a 42-week toxicity study.

One male at 2000 mg/kg dose level (446 mg Fe/kg/day) was euthanised for poor condition in Week 40. The animal was determined to have liver findings secondary to iron overload that was considered to be test-article related.

Dark faeces, black material in the GI tract, and microscopic findings of black granular material were present in all treated dogs (≥500 mg/kg in the 16-week study; ≥1000 mg/kg in the 42-week study). These were associated with unabsorbed test article.

In the 28-day and 33-day escalating dose studies, effects were limited to the GI system, and included unformed or bloody stool, and generally resolved with continued dosing; this was attributed to the development of tolerance in the GI tract.

Changes in serum parameters that were indicative of iron absorption were observed in the 16- and 42-week studies (but not in the 28-day study). Notably, statistically significant increases in serum iron, ferritin, and TSAT and decreases in TIBC were observed as doses ≥2000 mg/kg. By the end of the 42-week study, statistically significant increases in ferritin and decreases in TIBC were observed in males at 1000 mg/kg and a statistically significant increase in ferritin was also observed in females at 400 and 1000 mg/kg.

Decreased urinary phosphorus excretion was reported in all studies including this parameter for assessment. In the two studies of longer duration, repeated administration of ferric citrate in the diet for 16 or 42 weeks resulted in iron deposits in the liver, spleen, kidneys, lymph nodes, and the GI system. These findings were not reversed after the recovery period. These deposits resulted in evidence of tissue damage throughout the digestive tract, which included mucosal erosion and acute to subacute inflammation with subepithelial cleft formation and reactive epithelial hyperplasia in the oesophagus at doses of 2800 mg/kg (605 mg Fe/kg/day) for 16 weeks.

In the liver, microscopic findings including macrophages within chronic inflammatory foci and brown pigment accumulation at doses ≥500 mg/kg (108 mg Fe/kg/day), and bile duct proliferation and parenchymal fibrosis (males only) at doses ≥2000 mg/kg (446 mg Fe/kg/day) were observed. Additionally, at iron doses ≥1000 mg/kg (223 mg Fe/kg/day), statistically significant increases in ALT, AST, and ALP were noted after 16 weeks of dosing. These changes correlated with increases in absolute liver weights.

Based on the NOAEL dosage (400 mg/kg/day) in dog, the most sensitive species, the safety margin for the proposed human therapeutic dose of 200 mg/kg corresponds to 1.1.

2.4.4.1. Genotoxicity

No genotoxic potential was evidenced for FCCC in two *in vitro* genetic toxicology studies identified in the published literature: a bacterial reverse mutation test and a chromosomal aberration test conducted with Chinese hamster fibroblasts.

An evaluation of genotoxicity studies for various iron-containing compounds showed that none of the ferric compounds tested were positive in the bacterial reverse mutation test while ferrous sulphate, ferrous gluconate and ferrous fumarate exhibited positive responses under metabolic activation in bacterial reverse mutation assays with *S. typhimurium* tester strains TA1537, TA1538 and TA98, respectively. Ferrous lactate and ferrous sulphate were also positive in *in vitro* chromosomal aberration tests. In addition, ferrous fumarate yielded a positive response in the mouse lymphoma assay.

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, in fasting animals, a dose-related increase in nuclear aberrations was observed in the colon with no clear difference between ferric and ferrous compounds. A modest increase of nuclear aberrations of the colon was seen in fed animals only with ferrous sulphate. 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.

In vitro or *in vivo* studies conducted with citrate did not report any genotoxic potential.

The applicant concludes that according to the *in vivo* genotoxic studies with oral and intraperitoneal administrations of iron, FCCC, when taken orally with food, is expected to have a low genotoxic potential.

2.4.4.2. Carcinogenicity

In the published literature, two-year oral carcinogenicity studies following administration of FCCC, ferric chloride (in drinking water) and ferrous lactate (in the diet) showed no evidence of carcinogenicity. In addition, data from published life-time carcinogenesis studies have demonstrated that ferric citrate and other iron salts are also not carcinogenic in mice and rats when administered intramuscularly or subcutaneously. No carcinogenic effects have been evidenced in lifetime studies with citric acid.

2.4.4.3. Reproductive and developmental toxicity

No reproductive toxicity studies have been performed with FCCC. However, the applicant notes that KRX-0502 and JTT-751 had no toxic effects on the reproductive organs of rats and dogs after chronic oral treatment at doses up to 2800 and 2000 mg/kg/day, respectively.

Studies in rats with iron oxide and iron dichloride orally administered or with dextran-iron intramuscularly administered did not show adverse effects on reproductive performance.

Based on a series of studies in rats, no effects on reproduction were observed after oral administration of citric acid or sodium citrate.

Data from developmental studies with iron containing compounds (ferrous sulfate; ferrous gluconate; ferric pyrophosphate) conducted in chick embryos, mice and rats did not reveal teratogenic effects. In addition, several studies evaluating the developmental toxicity of citric acid concluded that citric acid is not a suspected teratogen.

No studies on post-natal development including maternal function have been conducted with KRX-0502 nor were such studies reported in the literature for oral administration of the iron and citrate moieties of the compound.

Systemic administration of iron dextran (20 mg/kg i.m., 6 injections in 3 weeks) to female rats before breeding for 5 consecutive generations, did not demonstrate effects on the reproductive parameters.

During three juvenile toxicity studies conducted in rat pups (PND21 to 76), test article-related effects included a decrease in mean body weight, changes in serum iron parameters consistent with increased iron absorption and changes in urinalysis (increase of incidence and severity of urine blood and protein measurements in males) and blood parameters (increase in alkaline phosphate, urea, creatinine in males and decrease in total protein and albumin in females). Microscopic findings of pigmented macrophages in several tissues were observed after a 56-day exposure, even after a 4-week recovery period.

The NOAEL was determined to be 1000 mg/kg/day in pups when FCCC was orally (diet) administered for up to 56 days on PND 21 to 76.

During a juvenile toxicity study conducted in rat pups (PND7), the NOAEL could not be determined when FCCC was orally (gavage) administered for 1 week based on mortality and adverse clinical signs observed in all groups (including the control group) related to the buffer chemical properties.

2.4.4.4. Toxicokinetic data

No standard pharmacokinetic/toxicokinetic studies were performed and typical parameters (i.e., C_{max}, AUC) were not measured. Instead, iron parameters have been reported in the toxicology studies.

2.4.4.5. Local Tolerance

FCCC is administered orally and its effects on the gastrointestinal tract were evaluated during the repeated-dose toxicology studies. No specific local tolerance studies were performed.

2.4.4.6. Other toxicity studies

On the basis of the evaluation of the effects of FCCC on the reticuloendothelial system organs and on the haematology of rats and dogs during the repeat-dose toxicity studies no immunotoxic effect is anticipated.

With respect to the impurities, a specification limit for one impurity is proposed. Potential toxicity of this impurity has been evaluated in rats and dogs repeat-toxicity studies. Literature data support the lack of genotoxicity of drug products containing this impurity.

The Applicant states that the potential for phototoxicity of FCCC is considered low.

2.4.5. Ecotoxicity/environmental risk assessment

The active ingredient in Xoanacyl is ferric citrate coordination complex. It is anticipated that upon release to the environment, the active substance will dissociate to ferric and citrate ions, both of which are naturally occurring and ubiquitously present in the environment. Therefore, FCCC that there is no expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

This product was previously authorised with the name of Fexeric for the control of hyperphosphataemia in adult patients with CKD. A similar dossier including the same seven repeat dose toxicity studies conducted in rats and in dogs has been provided.

The primary pharmacological effects of FCCC, i.e., increasing iron blood parameters and lowering serum and urine phosphate levels are supported by *in vitro* and *in vivo* pharmacodynamic literature studies in healthy and in mouse and rat models of CKD.

The Applicant did not conduct any specific safety pharmacology and secondary pharmacodynamic studies. However, this can be considered acceptable taking into account the well-known safety profile of the active substance and the available literature data. Moreover, CNS, respiratory and skeletal system safety was evaluated during toxicology studies in both rats and dogs. No concerning findings were reported.

Regarding pharmacokinetics, studies in rats and dogs showed that iron from FCCC was not significantly absorbed after oral administration for up to 28 days. However, in longer studies, the 13-week and 32-week in rats, and the 16-week and 42-week in dogs, serum iron and other iron parameters, as well as histopathological evaluations, indicated a dose-and time-dependent absorption of iron.

The submitted *in vitro* and *in vivo* DDI studies are identical to the documentation submitted for Fexeric and were considered acceptable in the previous evaluation (see EPAR for Fexeric). Nevertheless, the Applicant provided an updated version of interactions in 4.5, including several PK interactions present in other orally administered iron products on the market and supported by literature data.

As for toxicology, the target organ for primary toxicity of FCCC is the GI tract. In the dog's liver, microscopic findings included macrophages within chronic inflammatory foci and brown pigment accumulation, and bile duct proliferation and parenchymal fibrosis; correspondingly, increases hepatic enzymes and decreases of albumin and total bilirubin were seen. These observations were consistent with signs of iron accumulation.

Based on the NOAEL dosage (400 mg/kg/day) in the most sensitive species, the dog, the safety margin for the proposed human therapeutic dose of 200 mg/kg corresponds to 1.1. Although the safety margin is low, it is noted that the repeat-dose toxicity studies were performed in iron replete animals that bear little relation to the setting applicable to clinical practice namely, treatment of IDA in CKD patients.

In standard genotoxicity tests described in the literature, FCCC was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test), nor was it clastogenic in the chromosomal aberration test in Chinese hamster fibroblasts. Moreover, a low genotoxic potential of the iron moiety of KRX-0502 has been observed *in vivo*. No carcinogenic effects have been evidenced in lifetime studies with FCCC or citric acid. The Applicant notes that in all *in vitro* tests, iron was administered in a free ionic state, which is not representative of the way iron is present in the body. Iron present in a free ionic state may promote the formation of free radicals, which can be both cytotoxic as well as mutagenic. Under the test conditions, redox- cycling of free iron cannot be excluded and generation of reactive oxygen species may very well have affected the results in some of the genotoxicity studies.

Data from reproductive and developmental toxicological studies did not show any teratogenicity or adverse effects of iron salts on reproductive performance.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, FCCC is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

Overall, the nonclinical part of the dossier is considered acceptable and support the use of the product in the proposed indication.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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**

Table 1: Summary of studies providing pivotal evidence of efficacy

Study Number First subject Enrolled / Last Completed	**CKD Study Population**	**Design** **Location**	**Duration of Treatment Post-randomisation**	**Dosing**	**N Randomised / Treated**	**Efficacy Endpoints**
KRX-0502-204 Nov 2012 / Oct 2013 Phase 2	Subjects with IDA and elevated P, NDD (Hgb > 9.0 and < 12.0 g/dL, serum ferritin ≤ 300 ng/mL, TSAT ≤ 30%, serum P ≥ 4 and < 6 mg/dL)	Randomised, DBPC US	12 wks	Starting dose of 3 tablets/day (= 3 g as 1 g per tablet), dose titrated up or down based on serum P level. Max dose 12 tablets/day (=12 g)	Active = 75 / 75 Placebo = 74 / 73 Total = 149 / 148	**Co-primary**: changes from baseline to wk 12 in TSAT and serum P **Secondary**: changes from baseline to wk 12 in serum ferritin, Hgb, FGF23, urinary P, eGFR **Other**: changes from baseline to wk 12 in serum Ca × P, serum Ca, urinary Ca, serum CO_2/bicarb, UIBC, TIBC, serum iron, HCT, iPTH, FGF23

Study Number First subject Enrolled / Last Completed	**CKD Study Population**	**Design** **Location**	**Duration of Treatment Post-randomisation**	**Dosing**	**N Randomised / Treated**	**Efficacy Endpoints**
KRX-0502-306 Oct 2014 / Jan 2016 Phase 3	Subjects with IDA, NDD (Hgb ≥ 9.0 and ≤ 11.5 g/dL, serum ferritin ≤ 200 ng/mL and TSAT ≤ 25%, serum P ≥ 3.5 mg/dL)	Randomised, DBPC then OL extension US	DBPC period = 16 wks Extension period = 8 wks	Starting dose of 3 tablets/day (= 3 g as 1 g per tablet), dose titrated up or down based on Hgb level. Max dose 12 tablets/day (= 12g)	DBPC period: Active = 117 / 117 Placebo = 117 / 116 Total = 234 / 233 Extension period: Active = 167 / 167	**Primary**: % Hgb responders (increase of ≥ 1.0 g/dL at any point in 16 wks) **Secondary**: changes from baseline to wk 16 in Hgb, TSAT, serum ferritin, serum P, % with sustained Hgb response (mean change ≥ 0.75 g/dL over any 4-week period provided an increase ≥ 1.0 g/dL had occurred during this period), **Other**: changes from baseline to wk 16 in serum Ca, serum CO_2/bicarb, UIBC, TIBC, serum iron, HCT, eGFR, iPTH, FGF23, serum aluminium [c], % of subjects with mean change in Hgb ≥ 0.75 g/dL in last 4 wks, time to first Hgb increase ≥1.0 g/dL

Study Number First subject Enrolled / Last Completed	CKD Study Population	Design Location	Duration of Treatment Post-randomisation	Dosing	N Randomised / Treated	Efficacy Endpoints
KRX-502-304 Dec 2010 / Nov 2012 Phase 3	Subjects with HyperP, DD (HD 3 × weekly or PD) (serum P ≥ 2.5 mg/dL and ≤ 8.0 mg/dL prior to washout and ≥ 6.0 mg/dL after washout from existing phosphate-binding agents, serum ferritin < 1000 ng/mL, TSAT < 50%)	Randomised, OL, active-controlled [b] then randomised OL placebo-controlled for Xoanacyl arm US / Israel	Active-controlled period = 52 wks Placebo-controlled period = 4 wks	Starting dose of 6 tablets/day (1 g per tablet), dose titrated up or down based on serum P level. Max dose 12 tablets/day Active control: based on labelling	Active-controlled period: Active = 292 / 289 Active control = 149 / 149 Total = 441 / 438 Placebo-controlled period Active = 96 / 95 Placebo = 96 / 95 Total = 192 /190	**Primary**: change in serum P from wk 52 (end of active control period) to wk 56 (end of placebo-control period) **Secondary**: change to wk 52 in serum ferritin, TSAT, cumulative use of IV iron and ESA to wk 52, **Alternative (EMA)**: changes from baseline to wk 12 in serum P, Ca × P and serum Ca between the active and active control groups and between active and sevelamer carbonate groups (change in serum P at wk 12 between active and sevelamer carbonate was EMA primary) **Other**: change in serum Hgb, % serum P responders to different thresholds, vitamins (A, D, E, K B12), folic acid and lipids (LDL, HDL, triglycerides)

Study Number First subject Enrolled / Last Completed	CKD Study Population	Design Location	Duration of Treatment Post-randomisation	Dosing	N Randomised / Treated	Efficacy Endpoints

Ca = Calcium; DBPC = Double-blind Placebo-controlled; DD = Dialysis-dependent; eGFR = Estimated Glomerular Filtration Rate; EMA = European Medicines Agency; ESA = Erythropoietin Stimulating Agents; FGF23 = Fibroblast Growth Factor-23; HCT = Haematocrit; iFGF23 = Intact FGF23; HD = Haemodialysis; HDL = High Density Lipoprotein; Hgb = Haemoglobin; HyperP = Hyperphosphataemia; IDA = Iron Deficiency Anaemia; iPTH = Intact Parathyroid Hormone; IV = Intravenous; LDL = Low Density Lipoprotein; max = Maximum; N = Number of subjects in the treatment groups; NDD = Non-dialysis-dependent; OL = Open-label; P = Phosphorous; PD = Peritoneal Dialysis; TIBC = Total Iron-binding Capacity; TSAT = Transferrin Saturation; UIBC = Unsaturated Iron-binding Capacity; US = United States; wk/wks = Week/weeks
[a] Ferrous sulphate.
[b] calcium acetate or sevelamer carbonate or any combination of calcium acetate and sevelamer carbonate.
[c] Summary tables not generated as too few subjects with detectable levels of serum aluminium (Study 306 CSR Section 9.8.2).

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Absorption-distribution-elimination-excretion

Standard clinical pharmacokinetic studies have not been performed for Xoanacyl, nor were PK parameters measured in any clinical study. No information regarding the fate of iron and citrate after administration of the proposed product was provided, other than some literature studies regarding the mechanism of iron absorption mechanism, distribution and elimination.

Bioequivalence

The product to-be-marketed is planned to be manufactured by a different manufacturer compared to the product used in the clinical studies. No clinical study has been performed with the to-be-marketed product. The bridging of the to-be-marketed product to the product used in the clinical studies is based on *in vitro* data (see Quality AR).

Food effect

No formal food effect clinical studies have been conducted. Xoanacyl must be taken with food, not only to complex with dietary phosphate, but also to minimise GI adverse effects. The recommended dosing is with or immediately after meals. The dosing in all pivotal efficacy studies in the clinical program was with the patient's normal meals and so the efficacy profile reflects the taking of Xoanacyl per the intended dosing recommendations. In study 207, Xoanacyl at a lower dose of 1 or 2 g/day was taken separated from food by at least 2 hours whereas in studies with higher doses were given with food making interpretation difficult. The Applicant also states that the effect of food on the absorption of iron is well known. According to submitted literature studies, the administration of ferric salts with food results in decreased overall bioavailability of iron. Co-administration of food or supplements containing organic acids (e.g., ascorbic acid) can facilitate the conversion of Fe^{+3} to Fe^{+2}. However, the Applicant claims that the net effect of dietary constituents which enhance iron absorption is considered to be negligible, as the molar excess of ascorbic acid that would be required to increase iron bioavailability by a clinically relevant extent cannot be provided by food or clinical doses of vitamin supplements.

Dose proportionality and time dependencies

No dose proportionality or time dependency PK studies were performed.

Special populations

No formal PK studies were performed to assess the influence of hepatic function, gender, race, weight or age. All clinical studies were performed in patients with chronic kidney disease.

Pharmacokinetic interaction studies

The Applicant provided literature review considering iron binding with various drugs. A number of drugs, including tetracycline and its derivatives (e.g., doxycycline), penicillamine, levodopa, methyldopa, and ciprofloxacin, have functional chemical groups in a configuration that results in stable iron-drug complexes. These complexes have been shown to cause marked reduction in the extent of absorption and also the efficacy of the drug. The ferric form (Fe^{3+}) of iron generally binds much more strongly to compounds than the ferrous (Fe^{2+}) form due to its positive charge.

The *in vitro* interaction of 48 drugs with KRX-0502 by visual assessment at pH 1.2 mimicking the conditions of an empty stomach (Studies N° JTT751PK0003 and N° JTT751PK0005) and at pH 2.0, 4.5 and 6.8, mimicking the pH conditions of a fed stomach and the different parts of the gastrointestinal tract (Study N° 046715-02-01 [Protocol N° P15226-01]). These studies were conducted in the absence of phosphate.

Three *in vitro* studies were further conducted to investigate the potential for interaction, assessed by visual determination of any precipitate formed after incubating the test drug (in simulated human gastric fluid or in solutions at various pH levels [2.0, 4.5, and 6.8]) and ferric citrate together for 1 hour at 37°C. No precipitates were observed with 31 drugs: adefovir dipivoxil, amlodipine mesylate, atenolol, carvedilol, cetirizine 2 HCl, clonidine HCl, clopidogrel bisulfate, donepezil HCl, doxazosin mesylate, enalapril, famotidine, fluoxetine HCl, gabapentin, haloperidol, ibandronate sodium, ibuprofen sodium, isosorbide mononitrate, lansoprazole, losartan potassium, loxoprofen sodium, memantine HCl, metoprolol tartrate, nicardipine HCl, nicorandil, nizatidine, paroxetine HCl, penicillamine, pravastatin sodium, propranolol HCl, rimantadine HCl, theophylline, or tramadol HCl. Formation of precipitates was observed with 11 drugs: alendronate sodium, benserazide HCl, cefdinir (positive control), ciprofloxacin HCl, doxycycline hyclate, levodopa, levofloxacin HCl, methotrexate, sertraline HCl, valproate sodium, and vancomycin HCl. The compounds having positive precipitation results in the above studies were further tested for their DDI potential (except benserazide) with KRX-0502 in ten *in vitro* studies using validated HPLC methods for the measurement of drug recovery after incubation of each drug with 10 mg/mL KRX-0502 at pH 4.5 and 6.8 in the absence of phosphate (Studies N° 048590-02-01 to 048590-02-10). Two additional *in vitro* DDI studies were conducted, testing the time-course interaction of 16 drugs representative of the therapeutic classes of drugs usually used in CKD patients, up to 6 hours at pH 4.5 and 6.8 in the presence and in the absence of phosphate (Studies N° 053070-05-01 and WIL-106501). The Applicant concludes that these studies demonstrated that clinically meaningful interactions between KRX-0502 and levodopa, levofloxacin HCl, methotrexate or vancomycin HCl among the above molecules are unlikely.

Finally, six separate clinical DDI studies tested the potential interaction between KRX-0502 and ciprofloxacin, clopidogrel, glimepiride, losartan, diltiazem and digoxin in healthy volunteers.

Each study was a single-centre, open-label, randomised, 3-period, 3-way crossover DDI study to investigate the effect of multiple doses of Xoanacyl on the single-dose PK of the reference concomitant medication.

The study design for all studies was essentially identical, evaluating the concomitant drug alone (Treatment A), when taken with Xoanacyl and administered within 10 minutes of breakfast (Treatment B), or when taken with Xoanacyl and administered 2 hours after breakfast (Treatment C).

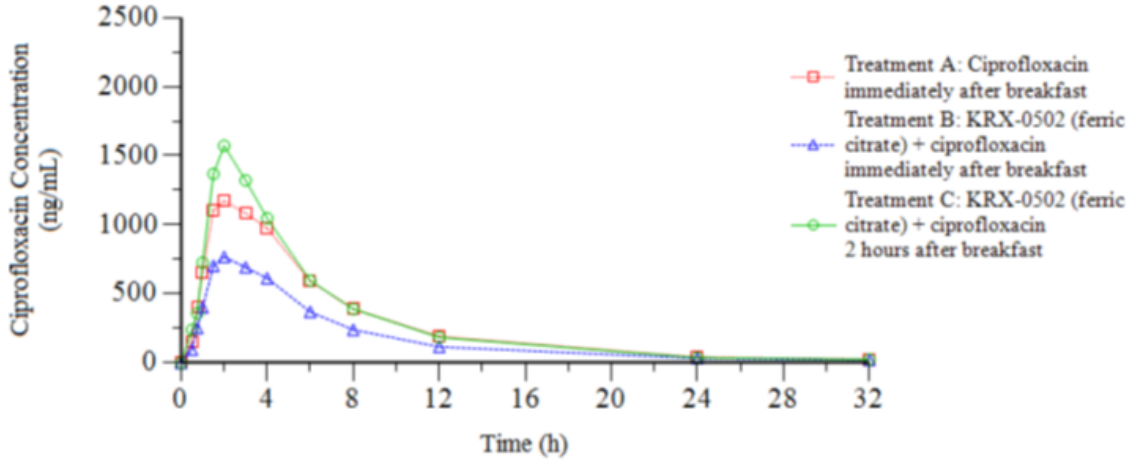
On Day -1 of Period 1, subjects were randomised in a ratio of 1:1:1 to 1 of 3 treatment sequences (ABC, BCA, and CAB). For each treatment the following was done:

- For Treatment A, subjects were required to fast overnight prior to their reference concomitant medication dose which was administered within 10 minutes following the completion of the moderate-fat breakfast on Day 1.
- For Treatments B on Day -1, subjects were required to fast for at least 1 hour prior to receiving their evening Xoanacyl dose at the start of their standard dinner. Subjects fasted overnight prior to the second dose of Xoanacyl dose which was administered at the start of a moderate-fat breakfast on Day 1. The reference concomitant medication dose was administered within 10 minutes following the completion of the breakfast. Subjects received their third dose of Xoanacyl at the start of their standard lunch on Day 1.
- For Treatment C, administration of Xoanacyl was identical to that described for treatment B and the reference concomitant medication was administered 2 hours following the completion of the breakfast.

The only observed DDI in these clinical studies was with ciprofloxacin, where a reduction in the peak and extent of absorption was observed when it was administered within 10 minutes of breakfast. Importantly, when administered 2 hours later, there was no impact Figure 2 as also suggested by literature studies where it was shown that administration of a quinolone antibiotic about 2 hours before or 3 hours after the ferrous sulphate did not result in significant reduction in absorption of the antibiotic agent (Allen et al., 2000).

For all other medications, there was no relevant different between the PK profile when taken alone with food compared to when taken with Xoanacyl and food.

Figure 2: Mean plasma ciprofloxacin concentrations vs time over a 32h period (linear scale) (n=26)



Note: KRX-0502 (ferric citrate) = FCCC. Source: Study KRX-0502-101 In-text Figure 1

To examine whether the use of concomitant frequently co-prescribed medications (fluoroquinolones, tetracyclines, proton pump inhibitors, thyroid hormones, sertraline, vitamin D, warfarin, aspirin) affects the efficacy of Xoanacyl, subgroup analyses from clinical study 304 of serum Pi level, TSAT, and ferritin levels were performed by the Applicant. The Applicant conducted a subgroup analysis in the DD CKD population, performed using the pivotal Study 304, and claims that the results do not indicate an

impact on the efficacy or safety profile of Xoanacyl for the 8 drugs evaluated (vitamin D, aspirin, proton pump inhibitor, warfarin, fluoroquinolones, thyroid hormone, sertraline or tetracyclines).

Thyroxine-based products (levothyroxine) have an established decreased absorption with iron-containing products (Campbell et al., 1992; Wiesner et al., 2021) and so for patients who are receiving this, there is a need to have the dose and response assessed to ensure the appropriate clinical outcome is achieved when taken concomitantly with AVA014. Finally, owing to the citrate in Xoanacyl, aluminium-based products should be avoided since citrate in known to increase the absorption of dietary aluminium (Gupta, 2014).

2.5.2.2. Pharmacodynamics

Mechanism of action

Xoanacyl has a dual mechanism of action; one associated with providing a source of ferric iron and one associated with decreasing the absorption of dietary phosphate thereby decreasing serum phosphorous.

Following oral administration, soluble ferric iron is reduced from the ferric to the ferrous form by ferric reductase in the GI tract. After transport through the enterocytes into the blood, oxidised ferric iron circulates bound to the plasma chaperone protein transferrin to sites of use, including for incorporation into Hgb, or stored as ferritin.

The remaining, non-absorbed compound in the GI tract reacts with dietary phosphate forming an insoluble complex that is excreted in the faeces. This decreases absorption of phosphate from the GI tract and hence lowers the levels of serum phosphorus.

The pharmacodynamics of Xoanacyl with respect to iron was evaluated using standard clinical parameters such as serum ferritin, TSAT as well as haemoglobin levels. In addition, parameters such total iron binding capacity, unsaturated iron-binding capacity and serum iron were also monitored in the clinical program. The most direct pharmacodynamic measure of the phosphate binding effect is the change in serum phosphorus levels.

Primary and Secondary pharmacology

Absorbed iron has been assessed in the clinical studies using a range of clinical parameters which were prospective endpoints. Serum ferritin levels provide an assessment of the level of iron stores in the liver, spleen, and bone marrow reticuloendothelial cells; TSAT levels provide an indication of the iron available for erythropoiesis; and serum iron and total iron binding capacity support a full picture of total iron status. These parameters are therefore used to provide information related to the systemic absorption from oral administration of Xoanacyl.

Increasing the Xoanacyl dose to 6 g/day or above appeared to increase the overall improvement from baseline in all iron parameters studied when compared to lower doses. Changes in serum phosphorous showed clear dose-dependent changes, reflecting its more direct mechanism of action in the GI tract.

No data are provided on that fate of citrate in the body following treatment as it is assumed that it will be absorbed and subjected to metabolism in the same way as the food constituent.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

No dedicated PK studies with the proposed product were performed. Instead, PD biomarkers were used to assess the performance of Xoanacyl. The proposed indication "for the treatment of iron deficiency anaemia in adult chronic kidney disease (CKD) patients with elevated serum phosphorus levels" is based on systemic absorption of iron, however it is acknowledged that complex homeostatic control mechanisms with maintenance of low levels of 'free' serum iron, and recycling of iron according to physiological requirements renders the interpretation of PK studies difficult. Therefore, the absence of a study is accepted. The Applicant provided a brief text in the SmPC Section 5.2 about the fate of iron and citrate in the body supported by literature.

No formal bridging studies can be performed with FCCC as the complex homeostatic mechanism of iron renders the interpretation of comparative bioavailability studies difficult. Therefore, bridging of the to-be-marketed product to the product used in the clinical studies was based on *in vitro* data (see Quality discussion).

The absence of dose proportionality or time dependency PK studies is acceptable considering the individual titration based on iron levels, existence of endogenous iron and the complexity of the homeostatic mechanisms that influence the absorption, storage, release render the interpretation of PK studies difficult.

No formal PK studies were performed in impaired renal function population, and this is accepted as all clinical studies were performed in patients with chronic kidney disease. The absence of formal PK studies to assess hepatic function, gender, race, weight or older age impact is accepted as these parameters are not expected to affect the PK of the proposed product.

Finally, the absence of formal PK studies with children is accepted as children are not included in the target population.

The applicant presented *in vitro* and *in vivo* investigations to study DDI interactions between the proposed product and other compounds. These DDI studies were considered acceptable (they were previously included in the MAA for Fexeric).

The applicant investigated the interaction potential of FCCC as a perpetrator considering the risk for complex binding between iron and other compounds. The only observed DDI in the clinical studies was with ciprofloxacin, where a reduction in the peak and extent of absorption was observed when it was administered within 10 minutes of breakfast. Importantly, when administered 2 hours later, there was no impact as also suggested by submitted literature studies. The Applicant described interactions in SmPC section 4.5, including several PK interactions present in other orally administered iron products on the market and supported by literature data. Additional literature submitted by the Applicant indicates that a time window of 2 to 3 hours between administration of iron containing products and "interacting" substances (e.g. Tetracyclines) can limit the interaction effect. The Applicant has provided relevant references justifying the 2-hour time restriction which applied to several structurally similar compounds to the ones tested.

The applicant discussed the potential effect FCCC could have locally on the pH of the stomach due to the high citrate content, by exploring two extreme scenarios (with the highest dose administered in minimum gastric volume and the lowest dose administered in maximum gastric volume). The expected concentrations from both scenarios were associated with pH values in the physiological gastric pH range in the fasted state and therefore are not expected to have a significant impact locally on the pH of the stomach. Additionally, the fact that each dose must be taken with a meal and therefore a

buffering effect of food will act on the final pH, further corroborates the limited impact FCCC could have locally on the pH of the stomach.

The subgroup analyses in clinical studies included a very small number of subjects and various confounding factors due to medical conditions that would lead to a subject requiring concomitant medications existed, deeming the sensitivity of these analyses as limited and the results uncertain. Therefore, the subgroups analysis is not included in Xoanacyl SmPC.

Pharmacodynamics

Xoanacyl has a dual mechanism of action; one associated with providing a source of ferric iron and one associated with decreasing the absorption of dietary phosphate thereby decreasing serum phosphorous. No studies specifically investigating clinical pharmacodynamics were conducted as standard pharmacodynamic markers for iron supplementation and phosphate binding ability respectively were primary endpoints in clinical trials.

The applicant considered that the characteristics of the FCCC complex are such that rapid uptake of citrate is unexpected under the conditions prevailing in the GI-tract. There is nevertheless some uptake of citrate which according to the applicant could be positive as it might provide an alkalising effect helping to balance chronic metabolic acidosis in patients with CKD. An increase in serum bicarbonate values over time in the NDD population (in average an increase with 1.57 mEq/L over the treatment period) as compared to placebo (0.2 mEq/L increase) was noted. The increase was more evident in patients with diabetes. In the DD-population, there was an increase in both study arms (test and active control) of the same magnitude in the test group in NDD population. Overall, a slight increase in bicarbonate levels was noted but not of a magnitude raising concerns.

2.5.4. Conclusions on clinical pharmacology

Overall, the PK is considered appropriate to support the proposed clinical use of Xoanacyl for the treatment of iron deficiency anaemia in adult chronic kidney disease (CKD) patients with elevated serum phosphorus levels. The mechanism of action is adequately described.

2.5.5. Clinical efficacy

2.5.5.1. Dose response studies

Although Xoanacyl is to be titrated based on clinical response, four fixed dose-ranging studies have been performed in the DD-population (Study 305, Study PBB00101, Study GBA2-1, and Study PNC00301) (Table 2).

Table 2: Dose-ranging studies (DD population) (compiled by assessor)

	Study design	Observational period	Dose FCCC (g/day)	Region
Study 305	Randomised OL	28 days	1, 6, or 8	USA
GBA2-1	DBPC	28 days	Placebo, 1.5, 3, or 6	Japan
PBB00101	DBPC	28 days	Placebo, 2, 4, or 6	US/Taiwan
PBB00101	DBPC	28 days	Placebo, 4, or 6	Taiwan

DBPC: Double-blind Placebo-controlled; OL: Open label

The dose-effect results from the dose ranging studies are presented in Table 3 (Study 305), Table 4 (GBA2-1), Table 5 (PBB00101), and Table 6 (PNC00301). The main parameter for the choice of starting dose in the pivotal clinical studies was serum phosphate in these dose-ranging studies. For the sake of conciseness, only data on serum phosphorus is therefore presented in the Overview. Full tables including results on serum ferritin and TSAT are presented in section 3.2 of the clinical AR.

Table 3: Change from baseline by dose group in study 305 for serum phosphorus (observed values in efficacy population) (truncated by assessor)

Parameter	Xoanacyl dose		
	1 g/day (N=50)	6 g/day (N=51)	8 g/day (N=45)
Serum phosphorus (mg/dL)			
Baseline, mean (SD) [a]	7.33 (1.737)	7.56 (1.727)	7.47 (1.631)
Week 4, mean change from baseline (SD)	-0.10 (1.285)	-1.86 (1.692)	-2.13 (1.998)
Comparison with 1 g/day [b] Mean difference 95% CI p-value	-	-1.52 (-1.98, -1.07) <0.0001	-1.94 (-2.41, -1.46) <0.0001
Comparison with 6 g/day [b] Mean difference 95% CI p-value	-	-	-0.41 (-0.88, 0.06) 0.0856

CI = Confidence Interval; SD = Standard Deviation;
[a] Baseline was defined as last assessment prior to study drug initiation.
[b] Pairwise compared with each other with p-value for testing mean difference equal to 0.
Source: Study KRX-0502-305 CSR, Table 12.1.2.1 (serum phosphorus),

Table 4: Change from baseline by dose group in study GBA2-1 for serum phosphorus (per protocol efficacy analysis set) (truncated by assessor)

Parameter	Placebo (N= 47 / 40)	JTT-751 dose		
		1.5 g/day (N = 47 / 42)	3 g/day (N = 48 / 50)	6 g/day (N = 43 / 27)
Serum phosphorus (phosphate) (mg/dL)				
Baseline (Day 0), mean (SD)	7.72 (1.13)	7.81 (1.10)	7.95 (1.25)	7.95 (1.39)
Week 4, mean change from baseline (SD)	0.04 (1.09)	-1.28 (1.15)	-2.16 (1.32)	-4.10 (1.09)
Comparison to placebo [a] p-value	-	<0.0001	<0.0001	<0.0001

Per protocol efficacy analysis set used for serum phosphorus (N=172)
SD=standard deviation; [a] p-value calculated using maximum contrast method compared to placebo. Source: Study GBA2-1 CSR Table 11-9 (serum phosphorus),

Table 5: Change from baseline by dose group in study PBB00101 for serum phosphorus (observed values in efficacy population) (truncated by assessor)

Parameter	Placebo (N=16)	FCCC dose		
		2 g/day (N=31)	4 g/day (N=32)	6 g/day (N=32)
Serum phosphorus (phosphate) (mg/dL)				
Baseline (Day 0), mean (SD)	7.2 (1.43)	7.2 (1.23)	7.1 (1.27)	7.3 (1.33)
Week 4, mean change from baseline (SD) [a]	-0.1 (2.02)	-0.3 (2.09)	-1.1 (1.57)	-1.5 (1.59)
Comparison to placebo [b] Mean difference 95% CI p-value	-	-0.2 (-1.6, 1.1) 0.7224	-1.1 (-2.2, 0.1) 0.0610	-1.5 (-2.6, -0.3) 0.0119

CI = Confidence Interval; SD = Standard Deviation;
[a] Includes early termination visit.
[b] Pairwise comparison to placebo with p-value for testing mean difference equal to 0.

Source: Study PBB00101 CSR Table 14.2.1 (serum phosphorus),

Table 6: Change from baseline by dose group in study PNC00301 for serum phosphorus (efficacy population) (truncated by assessor)

Parameter	Placebo (N =36 / 28)	FCCC dose	
		4 g/day (N =75 / 72)	6 g/day (N = 72 / 68)
Serum phosphorus (phosphate) (mg/dL)			
Baseline (Day 1), mean (SD)	7.371 (1.260)	6.964 (1.079)	6.952 (1.149)
Week 4, mean change from baseline (SD)	0.262 (1.146)	-1.381 (1.359)	-2.102 (1.604)
Comparison to placebo Mean difference 95% CI p-value [a]	-	-1.77 -2.7, -0.8 <0.001	-2.50 -3.4, -1.6 <0.001
Week 8, mean change from baseline (SD)	0.075 (1.510)	-1.595 (1.385)	-2.270 (1.289)
Comparison to placebo Mean difference 95% CI p-value [a]	-	-1.83 (-2.7, -1.0) <0.001	-2.51 (-3.4, -1.6) <0.001

CI = Confidence Interval; SD = Standard Deviation.
[a] ANCOVA model with a fixed effect for treatment group and baseline phosphate concentration as a covariate; mean difference is based on LS means and 95% CI is based on the model error term and LS means.
Source: Study PNC00301 CSR Table 14.2.1 (serum phosphorus)

In Study 305, the number of early terminations due to adverse events (AE) and treatment failures (TF) correlated and correlated inversely, respectively, with increased dose (1 g: AE: 2, TF: 9; 6 g: AE: 3, TF: 2; 8 g: AE: 8, TF: 3).

In Study GBA2-1, the primary reason for discontinuation was TSAT levels of 50% or more (25 subjects: 7, 8, 8 and 2 subjects in 1.5, 3, 6 g/day and placebo groups, respectively). Twelve subjects discontinued due to the serum phosphate level: 9 subjects in the 6 g/day group with <3 mg/dL [<0.97 mmol/L] and 3 subjects in the placebo group with ≥10 mg/dL [≥3.23 mmol/L]. AEs were reason of discontinuation in 3 subjects: 2 subjects in the 3 g/day group and 1 subject in the placebo group.

In total, 111/116 randomised and dosed patients (95.7%) were included into efficacy population of Study PBB00101. 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%). Treatment failure was not presented separately. This is not further pursued. Of the 8 subjects discontinuing due to AE, the number of subjects from the different treatment arms was 1, 4, 1, and 2 for placebo, 2 g/d, 4 g/d, and 6 g/d, respectively.

In Study PNC00301, all of the 183 enrolled subjects were randomised to one of three treatment groups (ferric citrate 6 g/day, N = 72; ferric citrate 4 g/day, N = 75; or placebo, N = 36) and received study treatment. In the placebo arm, 3 subjects discontinued due to AE, 1 due to phosphate > 9 mg/dL [2.91 mmol/L] and 2 due to TSAT > 55%. The corresponding numbers for the 4 g/d arm was 2, 1, and 3 subjects and for the 6 g/d 7, 0 and 3 subjects, respectively.

The applicant's Summary

Dose-dependent decreases in serum phosphorus levels and iron parameters suggested that a starting dose of 6 g/day of Xoanacyl would offer the best efficacy and safety balance for controlling hyperphosphataemia. Therefore, a starting dose of 6 g/day was chosen for Study 304 in the DD CKD population, and titration was allowed up to a maximum dose of 12 g/day to achieve the serum phosphorus goal of 3.5 to 5.5 mg/dL [1.13 - 1.78 mmol/L].

For Study 204 in subjects with CKD who were NDD, a starting dose of 3 g/day was chosen and titrated to a maximum of 12 g/day to achieve a serum phosphorus goal of 3.0 to 3.5 mg/dL [0.97 to 1.13 mmol/L]. The lower starting dose reflects that these subjects had a lower serum phosphorus and were not receiving dialysis, therefore a more cautious approach to a starting dose is appropriate. Results from Study 204 demonstrated that this dosing effectively controlled both iron-related and phosphorus-related parameters. The same dosing range was therefore used for Study 306, where Xoanacyl was titrated based on the Hgb level and the starting dose was also 3 g/day.

Additional support for a starting dose of 3 g/day in the NDD population comes from Study 207, a pilot study in NDD subjects, where a lower starting dose of 1 g/day and a maximum dose of 2 g/day was evaluated. However, this dosing resulted in a smaller Hgb increase, even though Xoanacyl was given without food to maximise its absorption.

2.5.5.2. Main studies

Three studies were determined to be pivotal for efficacy: Study 204 and Study 306 in the NDD-CKD (non-dialysis dependent chronic kidney disease) population and Study 304 in the DD-CKD (dialysis dependent chronic kidney disease) population (Table 1).

- **KRX-0502-204 (study 204):** 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.
- **KRX-0502-306 (study 306):** A Phase 3 Study of KRX-0502 (ferric citrate) for the Treatment of Iron Deficiency Anemia in Adult Subjects with Non-Dialysis Dependent Chronic Kidney Disease.
- **KRX-0502-304 (study 304):** A Three-Period, 58-Week Safety and Efficacy Trial of KRX-0502 (ferric citrate) in Patients with End-Stage Renal Disease (ESRD) on Dialysis.

Two of the pivotal studies, Study 204 and Study 304, were included in the MAA of Fexeric (EMEA/H/C/003776/0000).

Methods

The study designs of the three pivotal studies are summarised in Table 7.

Table 7: Summary of study design pivotal studies (compiled by assessor)

Design Feature	Study 204	Study 306	Study 304
Study Design	Randomised, DBPC:	Randomised, DBPC plus OLE,	Randomised, open-label, active-controlled period plus placebo-controlled period
Phase	Phase 2	Phase 3	Phase 3
Population	NDD CKD	NDD CKD	DD CKD
Study Duration	2-week Washout Period (if necessary), 12-week blinded Randomised Period	16-week blinded Randomised Period, 8-week OLE Period	1- to 2-week Washout Period, 52-week active-control, 4-week placebo control for subjects who received Xoanacyl in the active control period.
First Subject Enrolled / Last Completed	Nov 2012 / Oct 2013	Oct 2014 / Jan 2016	Dec 2010 / Nov 2012

DBPC = Double-blind Placebo-controlled; DD CKD = dialysis-dependent Chronic Kidney Disease; NDD CKD = Non-dialysis-dependent Chronic Kidney Disease; OLE = Open-label Extension

Study Participants

The study populations of the pivotal studies are summarised in Table 8.

Table 8: Summary of study populations in pivotal studies (compiled by assessor)

Design Feature	Study 204	Study 306	Study 304
Study Population	Adult subjects with NDD CKD Stage 3 to 5, IDA, and hyperphosphataemia after failing low phosphate diet (de novo or previously treated with phosphate binder)	Adult subjects with NDD CKD Stage 3 to 5 and IDA, who were intolerant of, or have had inadequate therapeutic response to oral iron supplements, in the opinion of the investigator	Adult subjects with DD CKD (on haemodialysis or peritoneal dialysis) receiving a phosphate binder for hyperphosphataemia
Sites	27 sites in the US	32 sites in the US.	58 study sites in the US 2 sites in Israel.
Time on Dialysis at Screening	None	None	≥ 3 months
eGFR at Screening	<60 mL/min/1.73m^2	<60 mL/min/1.73m^2; (≤ 20% of population with <15 mL/min/1.73m^2)	Not Applicable
Hgb at Screening	> 9.0 g/dL and <12.0 g/dL	≥9.0 g/dL and ≤ 11.5 g/dL	No threshold stipulated
TSAT at Screening	≤ 30%	≤ 25%	<50%
Ferritin at Screening	≤ 300 ng/mL	≤ 200 ng/mL	<1000 ng/mL
Serum Phosphorus Level at Screening; after Washout	≥ 4.0 mg/dL and < 6.0 mg/dL [1.29-1.94 mmol/l] after washout (or at screening if not on phosphate binder)	≥ 3.5 mg/dL [1.13 mmol/L]	≥ 2.5 mg/dL and ≤ 8.0 mg/dL [0.81-2.58 mmol/L] at Screening Visit; ≥ 6.0 mg/dL [1.94 mmol/L] after washout of phosphate binder
Therapies Discontinued Prior to Screening	Discontinued at least 8 weeks prior to screening: IV iron, blood transfusion. Discontinued at least 4 weeks prior to screening: ESA, cinacalcet; niacin; nicotinamide. Discontinued at screening: oral iron, phosphate binder	Discontinued at least 4 weeks prior to screening: IV iron, ESA, blood transfusion. Discontinued at screening: phosphate binders	Discontinued at screening: phosphate binders

DBPC = Double-blind Placebo-controlled; DD CKD = dialysis-dependent chronic kidney disease; eGFR = Estimated Glomerular Filtration Rate; ESA = Erythropoietin Stimulating Agents; Hgb = Haemoglobin; IDA = Iron Deficiency Anaemia; NDD CKD = non-dialysis-dependent chronic kidney disease; OLE = Open-label Extension

The inclusion criteria for ferritin was < 1000 ng/mL and TSAT < 50% in Study 304, and there was no threshold stipulated for baseline Hgb. Thus, the upper level for inclusion for ferritin is above the limits where dose reduction and discontinuation should be considered in the Xoanacyl SmPC. This is also in line with most recommendations, even though there is no established cut-off for ferritin where iron supplementation should be discontinued.

Study 204 exclusion criteria included:

- Recent or upcoming medical events that may influence the study outcome (parathyroidectomy within 24 weeks, symptomatic gastrointestinal (GI) bleeding or inflammatory bowel disease within 12 weeks, acute kidney injury or requirement for dialysis within 8 weeks prior to

Screening, or kidney transplant anticipated or start of dialysis expected with 16 weeks from Screening).

- Absolute requirement (in the opinion of the PI) for oral iron therapy, IV iron, ESA, blood transfusions, cinacalcet, vitamin C, or calcium-, magnesium-, or aluminium-containing drugs with meals.

Study 306 exclusion criteria included:

- Serum phosphorus <3.5 mg/dL [1.13 mmol/L] at Screening
- Liver enzymes (aspartate aminotransferase/alanine aminotransferase) >3 times upper limit of normal (ULN) at Screening.
- Recent or upcoming medical events that may influence the study outcome (symptomatic gastrointestinal (GI) bleeding or inflammatory bowel disease within 12 weeks, acute kidney injury or requirement for dialysis within 12 weeks prior to Screening, or kidney transplant anticipated or start of dialysis expected with 24 weeks from Screening).

Study 304 exclusion criteria included:

- Parathyroidectomy within 6 months prior to Screening Visit
- Actively symptomatic gastrointestinal bleeding or inflammatory bowel disease
- Serum phosphorus level ≥10.0 mg/dL [3.23 mmol/L] documented in all of the 3 monthly laboratories in all of the 3 months prior to the Screening Visit
- Absolute requirement for oral iron therapy, vitamin C, or calcium-, magnesium-, or aluminium-containing drugs with meals

Treatments

Xoanacyl was supplied as a 1 g tablet containing approximately 210 mg of ferric iron to those subjects randomised to ferric citrate. Matching placebo tablets were supplied to those subjects randomised to placebo (Study 204 and Study 306). Tablets were taken with meals.

In all studies except the 4-week extension period of study 306, the maximum dose was 12 g/d.

Treatments in the three pivotal studies are summarised in Table 9.

Table 9: Study treatments including allowed and prohibited medication in the pivotal studies (compiled by assessor)

Design Feature	Study 204	Study 306	Study 304
Comparator	Placebo	Placebo	52 wk active-controlled period: Calcium acetate, sevelamer carbonate, or any combination of the two, dosed and administered according to their label. 4 wk placebo-controlled period: Placebo
Starting dose	3 g/d	3 g/d	6 g/d
Titration	1 or 2 tablets increase/decrease to at wks 1, 2, 4, 6, 8, and 10 to	Randomised Period: 3 tablets increase at wks 4, 8, and 12 if no increase from baseline in Hgb	Increase (by 1 to 3 tablets/day) or decrease (by 1 tablet/day) at each

Design Feature	Study 204	Study 306	Study 304
	phosphate target 3.0 to 3.5 mg/dL [0.97-1.13 mmol/L]	of ≤ 1.0 g/dL and serum phosphorus was ≥ 3.0 mg/dL, otherwise no dose change. Extension Period: Restart with 3 tablets daily, 3 tablets increase to a maximum of 9 g/day at wks 18 and 20 if Hgb <11.5 g/dL and serum phosphorus ≥ 3.0 mg/dL.	visit to achieve target serum phosphorus of 3.5 to 5.5 mg/dL [1.13-1.78 mmol/L] Placebo-controlled period: dosing was continued, and dose adjustments made towards the same target.
Prohibited Concomitant Therapies During the Study	IV or oral iron; ESA; blood transfusion; phosphate binder other than study drug; vitamin C supplements; cinacalcet; niacin; nicotinamide; subjects absolutely requiring calcium-, magnesium-, or aluminium-containing drugs with food could not be enrolled	IV or oral iron; ESA; blood transfusion; phosphate binder other than study drug	Oral iron; phosphate binder other than study drug; vitamin C supplement; calcium-containing drug within 2 hours of food (also exclusion criteria for need to take magnesium or aluminium-containing drugs with food)
Allowed Concomitant Therapies During the Study	Vitamin D (or analogue), provided there were no changes to dose or frequency (max. dose of cholecalciferol 2000 IU daily); calcium supplements and water-soluble multivitamins could be taken at bedtime or ≥ 2 hours prior/after food	Not explicitly stated (those not prohibited)	IV iron if serum ferritin ≤ 1000 ng/mL or TSAT > 30%; ESA (or EPO) at the discretion of the Investigator; vitamin D (or analogue) and/or cinacalcet at the discretion of the Investigator; Ca supplements and water-soluble multivitamins containing small amounts of vitamin C at bedtime or ≥ 2 hours prior/after food

EPO = erytropoietin; ESA = erythropoiesis stimulating agents; Hgb = haemoglobin; IV = intravenous; TSAT = transferrin saturation; wk = week

The normal range for serum phosphate in adults is commonly given to 2.5 or 3 - 4.5 mg/dL (0.81 or 0.97 -1.45 mmol/L). The target interval in Study 204 is not fully in line with the current treatment recommendations in the KDIGO guideline updated in 2017, recommending "lowering elevated phosphate levels toward the normal range" rather than within (the lower part of) the normal range. This guideline was however not published during the planning and conduct of Study 204.

In the DD study 304, the use of IV iron and ESA was allowed. Due to an increased cardiovascular risk with normalising Hgb with the use ESA, the target level for Hgb under ESA treatment is typically around 10.5-11.5 g/dL. There was no guidance on adjustment of dosing of Xoanacyl based on Hgb levels in Study 304 (DD-population). Adjustments of IV iron and erythropoiesis stimulating agents (ESA) were left to the discretion of the investigators. IV iron was not recommended if the serum ferritin was >1000 ng/mL or the TSAT was >30%.

Handling of high levels of ferritin and/or low or very high levels of phosphate was specified in the studies. These are summarised below.

Study 204

- If a subject had serum phosphorus ≥6.0 mg/dL [1.94 mmol/L] for 2 visits in a row or 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.
- If Serum phosphorus <2.5 mg/dL [0.81 mmol/L], the study drug was held until reaching ≥ 3.0 mg/dL [0.97 mmol/L].

Study 306

- If a subject's Hgb was <9.0 g/dL for 2 visits in a row (at least 7 days apart) during the study after initiating the study drug, the subject was considered a treatment failure, stopped taking the study drug, completed the Termination Visit (with assessments as for Visit 11 or 14), and was discontinued from the study.
- If a subject's serum phosphorus was <2.5 mg/dL at any point during the study, the study drug dose was reduced temporarily. If a subject's serum phosphorus was <2.0 mg/dL, the study drug was temporarily discontinued, and restart of the study drug was done in consultation with Keryx and the Medical Monitor.
- Cases of rapid increases in iron storage parameters (i.e., TSAT ≥70% or serum ferritin ≥700 ng/mL) were reviewed on a case-by-case basis by the Medical Monitor, the Investigator, and Keryx, and if a dose adjustment was required, the subject was titrated down by 3 or more tablets per day until the increase resolved.

Study 304

- Subjects were considered treatment failures and were required to discontinue study drug if they were compliant with ≥80% compliant with 12 caplets/day of KRX-0502 or 12 capsules/tablets of calcium acetate and/or sevelamer carbonate for at least 2 visits in a row and had serum phosphorus levels of >8.0 mg/dL [2.58 mmol/L].
- Subjects were also considered treatment failures if they had adjusted serum calcium levels of>10.5 mg/dL, were in the active-control group receiving calcium acetate, and the PI elected to stop calcium acetate (after consultation with the CCC)
- If Serum phosphorus <2.5 mg/dL [0.81 mmol/L], the study drug was held until reaching ≥ 3.0 mg/dL [0.97 mmol/L].

Objectives

Study 204

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

Study 306

The primary objective of this study was to compare the efficacy and safety of KRX-0502 to placebo in the treatment of iron deficiency anaemia in adult subjects with NDD-CKD as measured by the percentage of subjects achieving an increase in haemoglobin (Hgb) of ≥1.0 g/dL at any study point between baseline and end of the Randomised Period (Week 16).

The secondary objective of this study was to determine the safety and tolerability of KRX-0502 in adult subjects with NDD-CKD as a treatment for iron deficiency anaemia.

Study 304

The primary efficacy objective of this study (for EMA) was to determine the non-inferiority of KRX-0502 as a treatment for hyperphosphataemia at Week 12 compared with sevelamer carbonate as single agent, and a comparison with combined active control (sevelamer and/or calcium acetate) was included as a supportive analysis.

Additional objectives were to determine the efficacy of KRX-0502 in improving iron stores as determined by serum ferritin and TSAT and in reducing use of IV iron and ESA compared to the active control during the 52-week active-controlled period.

Outcomes/endpoints

Study 204

In Study 204, the co-primary efficacy endpoints were tested in the following order to control for Type I error:

1. change in TSAT from Baseline to the end of Treatment Period (Week 12).
2. change in serum phosphorus from Baseline to the end of Treatment Period (Week 12).

Similarly, the following secondary endpoints in Study 204 were tested sequentially, with a comparison considered significant only if previous comparisons (including the co-primary endpoints) were significant:

1. change from Baseline to Week 12 in ferritin
2. change from Baseline to Week 12 in Hgb
3. change from Baseline to Week 12 in intact FGF23 (iFGF23)
4. change from Baseline to Week 12 in urinary phosphorus
5. change from Baseline to Week 12 in estimated glomerular filtration rate (eGFR).

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, unsaturated iron binding capacity (UIBC), total iron binding capacity (TIBC), serum iron, HCT, iPTH, C-terminal FGF-23.

Study 306

The primary efficacy endpoint for the study was the proportion of subjects achieving an increase in Hgb of ≥1.0 g/dL at any point between baseline and the end of the Randomised Period (Week 16).

The following endpoints were the secondary efficacy endpoints:

- Mean change in Hgb from baseline to end of the 16-week Randomised Period
- Mean change in TSAT from baseline to end of the 16-week Randomised Period
- Mean change in ferritin from baseline to end of the 16-week Randomised Period
- Proportion of subjects experiencing a sustained treatment effect on Hgb, defined as a mean change from baseline ≥0.75 g/dL over any 4-week time period during the Randomised Period, provided that an increase of at least 1.0 g/dL had occurred during that 4-week period
- Mean change in serum phosphorus from baseline to end of the 16-week Randomised Period

Study 304

The primary endpoint was the change in serum phosphorus levels from Week-52-baseline (Visit 21, Week 52) to the end of the placebo-controlled period (Visit 25, Week 56).

The alternative primary efficacy endpoint (primary efficacy endpoint for EMA) was difference in serum phosphorus, calcium × phosphorus product, and serum calcium between the KRX-0502 and all active

control groups and between KRX-0502 and sevelamer carbonate groups from Study-baseline (Visit 4) to Week 12 (Visit 11).

The following endpoints were the secondary efficacy endpoints:

- The change from Week-52-baseline in ferritin at Week 52 as compared with Study-baseline (Visit 4).
- The change from Week-52-baseline in TSAT at Week 52 as compared with Study-baseline (Visit 4).
- The cumulative IV iron administration from randomisation to Week 52 was compared.
- The cumulative ESA administration from randomisation to Week 52 was compared.

Sample size

Study 204

There were to be approximately 70 subjects randomised per treatment group.

It was assumed that the dropout rate during the 12-week treatment period was to be approximately 20%. Based on this, it had been expected that approximately 110 subjects were to complete 12 weeks of treatment with study drug: approximately 55 subjects in each treatment group.

Sample size estimation was based on the following assumptions: the baseline TSAT levels at visit 3 (day 0) was to be approximately 20% in both the treatment groups, the TSAT levels at visit 10 (week 12) was to be approximately 30% in the KRX-0502 (ferric citrate) group and 20% in the placebo group and the common standard deviation approximately 5%. Based on this, the study was to have at least 80% power to detect the hypothesised difference of 10 percentage points between the two groups (alpha = 0.05, two sided).

It had been anticipated that the baseline serum phosphorus at Visit 3 (Day 0) was to be approximately 4.5 mg/dL in both the KRX-0502 (ferric citrate) and placebo treatment groups while the ending serum phosphorus at Visit 10 (Week 12) was to be approximately 4.2 mg/dL in the KRX-0502 (ferric citrate) group and 4.5 mg/dL in the placebo group. The common standard deviation was assumed to be approximately 0.5 mg/dL. Based on these parameters, the study 204 was expected to have at least 80% power to detect the hypothesised difference of 0.3 mg/dL between the two groups (alpha = 0.05, two sided).

Study 306

Approximately 450 subjects were to be screened in order to randomise a total of approximately 230 subjects, approximately 115 subjects per treatment arm.

It had been anticipated that the proportion of subjects with an increase in Hgb ≥1.0 g/dL at any study point between baseline and through the end of the randomised period (Week 16) was to be approximately 32% for the KRX-0502 treatment group and 14% for the placebo treatment group (based on results of previous studies).

Using a two-sided alpha of 0.05, study 306 was expected to have at least 90% power to detect the hypothesised difference between the two groups.

Study 304

The primary objectives were long-term safety (after 52 weeks) and efficacy in the four-week, randomised, open-label placebo-controlled following the active-controlled period after 52 weeks of treatment.

The primary endpoint was change in serum phosphorus from baseline (Visit 21, Week 52) to end of the four-week placebo-controlled period (week 56).

The number of subject to be randomised was changed from 300 to approximately 350 (CSP version 3.0, amendment 2, 30 June 2011).

Approximately 350 subjects were to be randomised 2:1 to either KRX-0502, approximately 230 subjects, or active control group, approximately 120 subjects for the active controlled period. It had been assumed that up to 30% of the subjects in the KRX-0502 group would discontinue from the study before entering the placebo-controlled period, hence, approximately 140 to 160 subjects in the KRX-0502 group were planned to be re-randomised at a 1:1 ratio to receive either KRX-0502 or placebo.

This sample size was to provide at least 90% power to detect a treatment difference between ferric citrate and placebo at a 5% significance level, assuming that the treatment difference was 1.2 and the common standard deviation was 2.

Randomisation and blinding (masking)

Study 204

Subjects were randomised in a 1:1 ratio to the Xoanacyl group or the placebo group. Randomisation was to occur on or before visit 3 following completion of a 2-week washout period for subjects who were on a phosphate binder at screening, or immediately following the screening for subjects not taking a phosphate binder. Randomisation was conducted by IWRS. There were no stratifications employed.

All study personnel, including subjects, investigational sites, the central laboratory, and the medical monitor, were to be blinded to subject treatment codes throughout the study.

Study 306

At the Screening visit, enrolled subjects were assigned a unique subject number by IWRS (managed by Y-Prime), which was based on the site number and the sequential screening order of subjects.
At or before Visit 2, the site contacted the IWRS for assignment of a randomisation number for eligible subjects. Eligible subjects were randomised in a 1:1 ratio to receive Xoanacyl or matching placebo.

There were no stratifications employed.

To help preserve the blind during the randomisation period, all study personnel, including subjects, investigational sites, the central laboratory, sponsor personnel, and the medical monitor, were blinded to subject treatment codes throughout the study.

Study 304

During the active-controlled period, subjects were randomised in a 2:1 ratio to the Xoanacyl group or the active-control group of calcium acetate or sevelamer carbonate or any combination of calcium acetate or sevelamer carbonate at the discretion of the Investigator.

Subjects entering the 4-week placebo-controlled period were re-randomised in a 1:1 ratio to continue treatment with either Xoanacyl or placebo at the Final Visit for Safety (Week 52).

In order to randomise subjects, sites used IWRS managed by Bilcare Research Inc.

No blinding applied as this was an open-label study.

Statistical methods

Study 204

The Intent-to-Treat (ITT) population was to consist of all subjects who were randomised, had a baseline laboratory value, had taken at least one dose of study drug, and had at least one post-baseline laboratory value. This was the analysis set used for the efficacy analysis.

The two primary efficacy endpoints were to be analysed using an ANCOVA model with treatment as a fixed effect and baseline value of the endpoint being analysed as the covariate. Missing efficacy data was to be imputed using last observation carried forward (LOCF) method for the primary analyses on the primary efficacy variables. In those cases where a subject had discontinued prematurely, including treatment failures, the subject's most recent value was to be considered to have remained unchanged through the end of the 12-week Treatment Period.

All the secondary endpoints were to be similarly analysed as the primary endpoints using an ANCOVA model with treatment as a fixed effect and baseline value of the endpoint being analysed as the covariate.

Supportive sensitivity analyses were to be performed for the primary efficacy endpoint, and the secondary efficacy endpoints based on Mixed Model Repeated Measures (MMRM) methods. Missing values were to remain as missing: there was no attempt made to impute missing values. The model was to include terms for treatment group, baseline value, weeks post baseline, treatment by weeks post baseline interaction.

Study 306

The Intent-to-Treat (ITT) population was to consist of all subjects who were randomised, had a baseline laboratory value, had taken at least one dose of study treatment, and had at least one post-baseline laboratory assessment during the Randomised Period.

This was the main analysis set for the efficacy analyses.

The primary efficacy endpoint was the proportion of subjects achieving an increase from baseline in Hgb of ≥1.0 g/dL at any study point through the end of the randomised period (Week 16). Subjects who discontinued the trial during the randomised period prior to achieving an increase from baseline in Hgb of ≥1.0 g/dL were to be considered non-responders.

The between group comparison for the primary efficacy variable was to be analysed using a two-sided chi-square test. The estimated proportions for the treatment groups and the two-sided 95% confidence interval for the treatment difference will be calculated via normal approximation.

For the secondary endpoints defined as the difference in mean change from baseline to week 16/at week 16: a Mixed Model Repeated Measures (MMRM) with the corresponding baseline value as a covariate was to be fit with treatment, week, and treatment by week interaction as fixed effects and subject as a random effect. Missing values for variables to be analysed using Mixed Model Repeated Measures (MMRM) models were not to be imputed.

The primary analysis of the primary endpoint was to be repeated for the PP population as a sensitivity analysis.

Sensitivity analyses were also planned for secondary endpoints. Sensitivity analyses for continuous secondary endpoints used an analysis of covariance (ANCOVA) model based on last observation carried forward (LOCF) methodology.

Study 304

The primary efficacy analysis set was the Full Analysis Set (FAS). FAS was to include of all subjects who took at least one dose of study medication and had a baseline and at least one post-baseline serum phosphorus value.

The primary efficacy endpoint was the change in serum phosphorus from baseline (Visit 21, Week 52) to end of the four-week placebo-controlled period (Visit 25, Week 56) versus placebo. The primary efficacy variable was to be analysed using an ANCOVA model with treatment as the fixed effect and Week-52 baseline as the covariate.

The primary efficacy analysis as requested by the EMA, was a non-inferiority analysis at Week 12 of the change from Study-baseline in serum phosphorus comparing KRX-0502 to sevelamer carbonate as single agent. This analysis was performed using ANCOVA and LOCF for missing data.

Four secondary endpoints had been defined. They were all to be analysed week 52 compared to the active comparator.

Supportive sensitivity analyses were to be performed for both the primary, and the secondary efficacy endpoints using Mixed Model Repeated Measures (MMRM) models. During the placebo-controlled period all missing values were to remain as missing.

Multiplicity control

All three studies used the same approach to define a multiple testing procedure.

To control the overall type I error rate at 5%, a gatekeeping sequential strategy (Alex Dmitrienko, 2004; Dmitrienko, Offen, Westfall, 2003) was to be applied. The primary efficacy endpoint was to be tested first and if significant the testing of secondary efficacy endpoints was to follow according to the predefined order. Each of the comparisons were to be made at a type I error rate of 5%. Any comparison was to be eligible for superiority testing only if all previous comparisons were significant in favour of active treatment.

No interim analysis had been planned in any of the studies.

Results

Participant flow

In all three studies, the proportion of screened subjects not enrolled in the study was high (Study 204: 250/399 [63%], Study 306: 411/645 [64%]; Study 304: 631/1072 [59%]). For all studies, the main reason was that the subject did not qualify for enrolment based on the inclusion and exclusion criteria, including washout failure. Since the subjects were not yet randomised, this was not expected to impact study conduct or study outcome.

Study 204

The subject disposition is presented in Table 10.

Table 10: 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 randomised 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%)
Haemoglobin <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 haemoglobin <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).

One placebo subject was randomised but never received a dose of study drug due to withdrawn consent and was therefore excluded from the safety population.

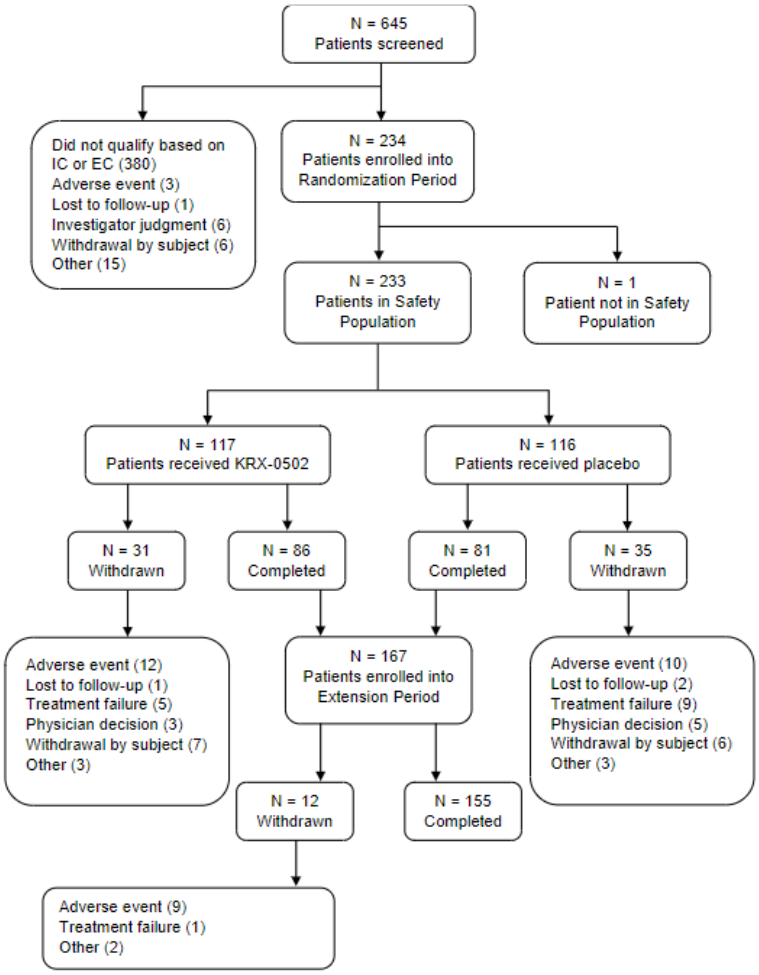
Three subjects randomised to receive Xoanacyl, and 5 subjects randomised to receive placebo were excluded from the ITT population since they did not meet the criteria for inclusion into the ITT population (had taken at least 1 dose of study drug and had at least one post-baseline laboratory value). The reasons for this were withdrawn consent (placebo: n=3, Xoanacyl: n=2) and adverse events (placebo: n=2, Xoanacyl: n=1).

Early termination was more common in the placebo versus the Xoanacyl arm. This was mainly driven by treatment failure, i.e., having serum phosphorus ≥6.0 mg/dL or haemoglobin <9.0 g/dL for 2 consecutive study visits (11/74 for placebo versus 1/75 for Xoanacyl). Out of the 11 subjects with treatment failure in the placebo arm, 9 subjects failed the haemoglobin criterium. This may be indicative of a treatment effect. Early termination due to adverse events was more common in the AV 1014 arm.

Study 306

Subject disposition and reasons for withdrawal in Study 306 are provided in Figure 3Figure 3.

Figure 3: Participant flow Krx-0502-306



Note: One subject in the KRX-0502 group shown under "withdrawal by subject" for the Randomised Period completed Visit 11 at Week 16, but then withdrew consent and was not enrolled into the Extension Period. The subject was therefore considered withdrawn during the Randomised Period.
EC=exclusion criteria; IC=inclusion criteria

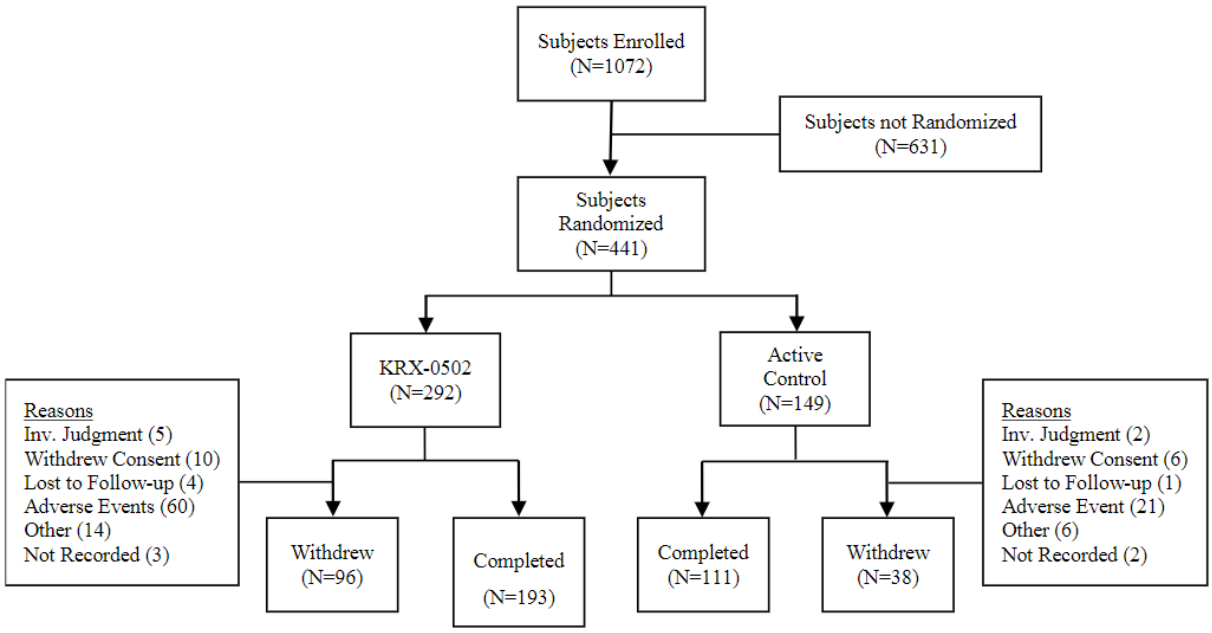
One placebo subject was randomised but never received a dose of study drug (withdrawal by subject) and was therefore excluded from the safety population.
Another subject in the placebo arm discontinued prior to a post-baseline laboratory assessment (adverse event [pneumonia, urinary retention], physician's decision) and was excluded from both the safety population and the ITT Population.

In this study, early withdrawal was similar in both treatment arms.

Study 304

Subject disposition and reasons for withdrawal during the active-controlled period and the placebo-controlled period are provided in Figure 4 and Figure 5, respectively.

Figure 4: Subject disposition and reasons for withdrawal in active-controlled period of study 304



Sources:
Note: Four subjects originally randomised to active control during the active-controlled period were switched to KRX-0502 due to hypercalcemia.
Inv.=Investigator; KRX-0502=ferric citrate; N=number of subjects.

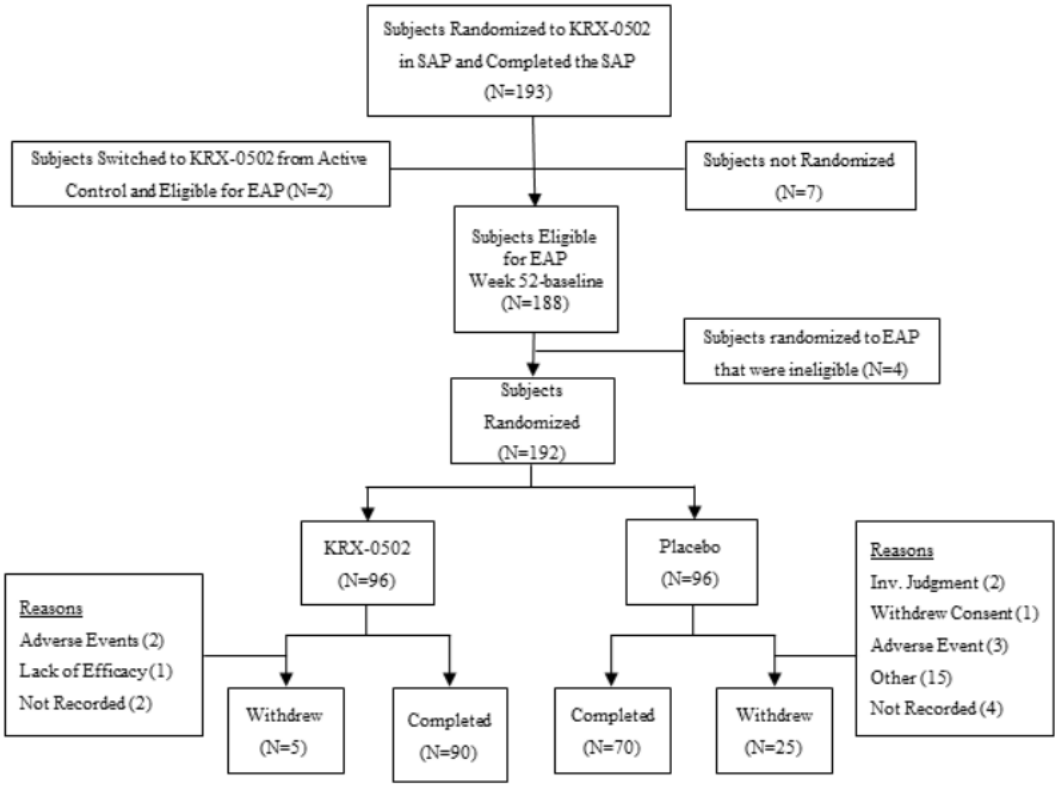
Subjects excluded from the Safety population and from the full analysis set (FAS) in active-controlled period

There were 3 subjects, all in the Xoanacyl treatment arm, who did not receive study treatment and were thus not included in the safety population. Furthermore, 8 subjects in the Xoanacyl arm and 3 subjects in the Active control arm were not included in the FAS. Upon request, the Applicant clarified that 14/289 (4.8%) subjects in the Xoanacyl treatment arm and 7/149 (4.7%) in the control arm were recorded as treatment failures.
All subjects in the Xoanacyl arm and two subjects in the control arm reached the stipulated threshold of >8.0 mg/dL for 2 consecutive visits. These subjects discontinued study drug but complete study visits and could be started on another phosphate binder at the discretion of the investigator.
The remaining five subjects in the control arm, all on calcium containing phosphate binders, reached the threshold for adjusted serum calcium >10.5mg/dL and were switched to Xoanacyl. These subjects were also to continue in the study.

Randomisation to placebo-controlled period

In the end of the active-controlled period, 195 subjects were eligible for randomisation to the placebo-controlled period; 193 originally randomised to Xoanacyl and two who switched from active control during active-controlled period. Of these, 188 were randomised. An additional four subjects were erroneously randomised to the placebo-controlled period. These subjects were ineligible for randomisation since they had not completed the active-controlled period but were included in the 192 randomised subjects. Two of these subjects were originally randomised to active control during the active-controlled period.

Figure 5: Subject disposition and reasons for withdrawal in placebo-controlled period of study 304



Note: Four subjects originally randomised to active control during the active-controlled period were switched to KRX-0502 due to hypercalcemia. Two of these subjects completed the active-controlled period and were eligible for randomisation to the placebo-controlled period. The other two subjects did not complete the active-controlled period and were ineligible to be randomised to the placebo-controlled period but were randomised.
Inv.=Investigator; KRX-0502=ferric citrate; N=number of subjects

The majority of the "Other" events are due to a serum phosphorus level ≥9.0 mg/dL [2.91 mmol/L].

Recruitment

The dates for First patient enrolled ("randomised" for study 304) and Last patient contact are summarised in Table 11.

Table 11: Recruitment periods for the three pivotal studies (complied by assessor)

	Study 204	**Study 306**	**Study 304**
First subject enrolled	16 November 2012	03 October 2013	22 December 2010
Last patient contact	29 October 2013	15 January 2016	07 November 2012

Conduct of the study

A more comprehensive summary of protocol amendments and protocol deviations is presented in Clinical AR section 3.3.1.3.1.

Protocol amendments

In Study 204, the protocol was amended four times. Two of the amendments were made prior to study initiation and a third on the same date as the first subject was enrolled.

The fourth protocol amendment in study 204 is dated 01 May 2013, i.e., halfway through the study. In this amendment, serum ferritin was downgraded from the third component of the co-primary endpoint to the first secondary endpoint. At this time point, approximately half of the study population was enrolled, and given the short observation time, a non-negligible part of the study population would have completed the study. This change of the co-primary endpoint was not justified.
Most other alterations in the fourth amendment aimed at increasing enrolment, including increased number of study sites, increased number of subjects allowed per site, increased enrolment period and widening the inclusion criteria for Hgb from ≥9.5 - ≤11.0 g/dL to ≥9.5 - ≤11.5 g/dL.

The protocol of Study 306 was amended twice, once prior to study initiation and once approximately 6 weeks after first subject enrolment. The second amendment included for example a safety consideration to allow an increase in study drug dose per the titration schedule only if serum phosphate is ≥3.0 mg/dL and an additional exclusion criterion, excluding subjects with active infection requiring antibiotics at Screening.

The protocol of Study 304 was amended once prior to study initiation and once approximately six months after the first subject enrolment. One of the changes was introducing the option to switch a subject from active control to treatment with KRX-0502 if developing hypercalcemia on either calcium acetate as a single agent or in the combination of calcium acetate and sevelamer carbonate. The number of subjects to be randomised was raised from 300 to 350, and monitoring of iron parameters was increased.

Protocol deviations

The number of protocol deviation was high in Study 304, where 784 protocol deviations, including 196 IV iron-related protocol deviations, were reported. This was discussed during the MAA procedure for Fexeric, where the Applicant was asked to justify the absence of impact of these protocol deviations to both efficacy and safety. In response to this request the Applicant performed and additional analysis for efficacy and safety for four types of major protocol deviations, defined as (1) drug dosing deviations, (2) deviations related to following up on clinical laboratory evaluations for dose adjustments, (3) missed assessments potentially related to safety or that may confound analysis of Safety/Efficacy, (4) markedly different washout periods, and (5) Inclusion/Exclusion criteria deviations that were not purely minor delays in lab value. These analyses were based on Study 304 and with serum phosphate as efficacy measure.
A post-hoc sensitivity analysis excluding all subjects with major protocol deviations showed a trend against a stronger treatment effect on serum phosphate during the first 12 weeks. Assessing the safety, patients with and without major protocol deviations had comparable proportions of AE in Xoanacyl arm of Study 304.

In Study 204 and Study 306, the number of protocol deviations was lower.
In Study 204, 41 "non-laboratory related" protocol deviations occurred in 26 subjects during the study.
In Study 306, a total of 43 major protocol deviations occurred during screening or the Randomised Period in 39 out of 234 subjects randomised. The most frequently occurring major protocol deviation was "overall compliance less than 80%".

Baseline data

The summary of demographic and other Baseline characteristics across the 3 pivotal efficacy studies is provided in Table 12.

Table 12: Summary of baseline characteristics in pivotal efficacy studies (amended by assessor)

Parameter	Study 204 (NDD)		Study 306 (NDD)		Study 304 [a] (DD)	
	Xoanacyl (N=75)	Placebo (N=73)	Xoanacyl (N=117)	Placebo (N=116)	Xoanacyl (N=289)	Active control (N=149)
Age						
Mean years (SD)	65.8 (12.15)	64.5 (13.55)	65.6 (11.15)	65.2 (13.08)	54.8 (13.38)	53.7 (13.01)
< 65 years, n (%)	31 (41.3%)	34 (46.6%)	48 (41.0%)	48 (41.4%)	227 (78.5%)	121 (81.2%)
≥ 65 years, n (%)	44 (58.7%)	39 (53.4%)	69 (59.0%)	68 (58.6%)	62 (21.5%)	28 (18.8%)
Sex, n (%)						
Male	24 (32.0%)	28 (38.4%)	41 (35.0)	45 (38.8)	181 (62.6%)	87 (58.4%)
Female	51 (68.0%)	45 (61.6%)	76 (65.0)	71 (61.2)	108 (37.4%)	62 (41.6%)
Race						
Asian	0	1 (1.4%)	1 (0.9%)	1 (0.9%)	0	1 (0.7%)
Black or African American	16 (21.3%)	16 (21.9%)	38 (32.5%)	31 (26.7%)	154 (53.3%)	78 (52.3%)
White/Caucasian	59 (78.7%)	56 (76.7%)	78 (66.7%)	82 (70.7%)	121 (41.9%)	62 (41.6%)
American Indian or Alaskan native	0	0	0	2 (1.7%)	2 (0.7%)	1 (0.7%)
Native Hawaiian or Pacific Islander	0	0	0	0	0	2 (1.4%)
Other/unknown	0	0	0	0	12 (4.3%)	5 (3.4%)
Weight, kg						
Mean (SD)	88.4 (21.1)	89.9 (24.7)	94.9 (23.3)	91.9 (23.6)	93.4 (27.5)	89.6 (24.0)
CKD stage, n (%)						
Entry criterion	3 to 5		3 to 5		Stage 5 by default (all DD)	
Stage 3	14 (18.7%)	16 (21.9%)	50 (42.7%)	62 (53.4%)	NA	NA
Stage 4	39 (52.0%)	39 (53.4%)	53 (45.3%)	45 (38.8%)	NA	NA
Stage 5	21 (28.0%)	17 (23.3%)	14 (12.0%)	9 (7.8%)	NA	NA
Other/missing	1 (1.3%)	1 (1.4%)	0	0	NA	NA
Dialysis status						
Entry criterion	No dialysis		No dialysis		Haemodialysis 3 times a week or peritoneal dialysis	
Haemodialysis, n (%)	NA	NA	NA	NA	269 (95.7%)	142 (97.3%)
Peritoneal dialysis, n (%)	NA	NA	NA	NA	11 (3.9%)	3 (2.1%)
eGFR, mL/min/1.73m^2						
Entry criterion	< 60		< 60		NA (all DD)	
Mean (SD)	25.8 (11.48)	22.6 (9.16)	27.8 (13.02)	29.5 (12.78)	NA	NA
Hgb, g/dL						
Entry criterion	> 9 and < 12		≥ 9.0 and ≤ 11.5		No threshold stipulated	
Mean (SD)	10.5 (0.81)	10.6 (1.07)	10.44 (0.73)	10.38 (0.78)	11.61 (1.24)	11.71 (1.26)
TSAT, %						
Entry criterion	≤ 30		≤ 25		< 50	
Mean (SD)	21.6 (7.44)	21.0 (8.26)	20.2 (6.43)	19.6 (6.63)	31.3 (11.21)	30.8 (11.57)
Serum ferritin, ng/mL						
Entry criterion	≤ 300		≤ 200		< 1000 ng/mL	
Mean (SD)	115.8 (83.11)	110.0 (80.88)	85.9 (55.74)	81.7 (58.26)	592.80 (292.86)	609.50 (307.69)
Serum phosphorus, mg/dL						
Entry criterion	≥ 4 and < 6 after washout, or if not on phosphate binder		not < 3.5 mg/dL (so ≥3.5)		≥ 6 after washout (and not ≥ 10)	
Mean (SD)	4.5 (0.61)	4.7 (0.60)	4.23 (0.91)	4.12 (0.68)	7.41 (1.63)	7.56 (1.74)
Serum phosphorus, mmol/L (derived from mg/dL value using conversion factor of 0.3229)						
Entry criterion	≥ 1.29 and 1.94 after washout, or if not on phosphate binder		≥1.13		≥ 1.94 after washout (and not ≥ 3.23)	

Parameter	Study 204 (NDD)		Study 306 (NDD)		Study 304 [a] (DD)	
	Xoanacyl (N=75)	Placebo (N=73)	Xoanacyl (N=117)	Placebo (N=116)	Xoanacyl (N=289)	Active control (N=149)
Mean (SD)	1.45 (0.20)	1.52 (0.19)	1.37 (0.29)	1.33 (0.22)	2.39 (0.53)	2.44 (0.56)
iFGF23, mg/dL						
Entry criterion	No threshold stipulated		No threshold stipulated		No threshold stipulated	
Mean (SD)	319.0 (577.48)	263.2 (226.30)	340.3 (1119.16)	324.0 (878.65)	Not assessed	Not assessed

Numbers analysed

Parameter	Study 204 (ITT)		Study 306 (ITT)		Study 304 (FAS)	
	Xoanacyl (N=75)	Placebo (N=73)	Xoanacyl (N=117)	Placebo (N=116)	Xoanacyl (N=289)	Active control (N=149)
ITT/FAS	72	69	117	115	281	146

The definition for FAS in Study 304 was "all subjects who took ≥1 dose of study medication and had a baseline and at least 1 post-baseline serum phosphorus value". The definition for ITT in Study 204 and Study 306 was "all subjects who took ≥1 dose of study medication and had a baseline and at least 1 post-baseline laboratory value".

Outcomes and estimation

Study 204

A summary of the results from the co-primary and secondary endpoints is presented in Table 13.

Table 13: Summary of results from primary and secondary endpoints - study 204

Parameter		Placebo (N=69)	Xoanacyl (N=72)
Serum TSAT, % (Co-primary)	**Baseline**		
	Mean (SD)	21.0 (8.26)	21.6 (7.44)
	Week 12, change from baseline		
	LS mean (SE)	-1.1 (1.20)	10.2 (1.18)
	Difference to placebo (SE)	-	11.3 (1.70)
	p-value	-	<0.001
Serum phosphorus, mg/dL (Co-primary)	**Baseline,**		
	Mean (SD)	4.7 (0.60)	4.5 (0.61)
	Week 12, change from baseline		
	LS mean (SE)	-0.2 (0.07)	-0.7 (0.07)
	Difference to placebo (SE)	-	-0.5 (0.10)
	p-value	-	<0.001
Serum ferritin, ng/mL (Secondary)	**Baseline**		
	Mean (SD)	110.0 (80.88)	115.8 (83.11)
	Week 12, change from baseline		
	LS mean (SE)	-4.2 (7.67)	73.3 (7.51)
	Difference to placebo (SE)	-	77.5 (10.83)
	p-value	-	<0.001
Haemoglobin, g/dL (Secondary)	**Baseline**		
	Mean (SD)	10.6 (1.07)	10.5 (0.81)
	Week 12, change from baseline		
	LS mean (SE)	-0.2 (0.10)	0.4 (0.10)
	Difference to placebo (SE)	-	0.6 (0.14)
	p-value	-	<0.001
iFGF-23, pg/mL (Secondary)	**Baseline**		
	Mean (SD)	263.2 (226.30)	319.0 (577.48)
	Week 12, change from baseline		
	LS mean (SE)	17.4 (37.10)	-108 (36.21)
	Difference to placebo (SE)	-	-125 (52.42)
	p-value	-	0.017
Urinary phosphorus, mg/24 hours (Secondary)	**Baseline**		
	Mean (SD)	726.9 (280.53)	730.1 (286.08)
	Week 12, change from baseline		
	LS mean (SE)	17.5 (33.67)	-269.0 (32.33)
	Difference to placebo (SE)	-	-287.0 (47.15)
	p-value	-	<0.001
eGFR, mL/min/1.73 m² (Secondary)	**Baseline**		
	Mean (SD)	25.8 (11.48)	22.6 (9.16)
	Week 12, change from baseline		
	LS mean (SE)	1.6 (0.79)	-0.3 (0.76)
	Difference to placebo (SE)	-	-1.9 (1.11)
	p-value	-	0.079

The primary efficacy variables were analysed using an ANCOVA model with treatment as a fixed effect and baseline value of the endpoint being analysed as the covariate.
Sensitivity analyses using a mixed model for repeated measures (MMRM) model with terms of treatment group, baseline value, weeks post baseline, treatment by weeks post baseline interaction was performed for the co-primary and secondary endpoints.
For all endpoints, results of the sensitivity analysis were similar to the results from ANCOVA.

Study 306

The primary efficacy endpoint for the study was the proportion of subjects achieving an increase in Hgb of ≥1.0 g/dL at any point between baseline and the end of the Randomised Period (Week 16).

A summary of the results from the primary and secondary endpoints is presented in Table 14.

Table 14: Summary of results from primary and secondary endpoints in Study 306

Parameter		Placebo (N=115)	Xoanacyl (N=117)
Haemoglobin responders, % (Primary)	**During randomised period**		
	% of subjects	19.1	52.1
	Difference to placebo (95% CI)	-	33.0 (21.4, 44.6)
	p-value	-	<0.001[a]
Sustained haemoglobin responders, % (Secondary)	**During Randomised Period**		
	% of subjects	14.8	48.7
	Difference to placebo (95% CI)	-	33.9 (22.8, 45.1)
	p-value	-	<0.001[a]
Haemoglobin, g/dL (Secondary)	**Baseline**		
	Mean (SD)	10.38 (0.78)	10.44 (0.73)
	Week 16, change from baseline		
	LS mean (SE)	-0.08 (0.10)	0.75 (0.09)
	Difference to placebo (SE)	-	0.84 (0.13)
	p-value	-	<0.001[b]
TSAT, % (Secondary)	**Baseline**		
	Mean (SD)	19.6 (6.63)	20.2 (6.43)
	Week 16, change from baseline		
	LS mean (SE)	-0.6 (1.37)	17.8 (1.37)
	Difference to placebo (SE)	-	18.4 (1.94)
	p-value	-	<0.001[b]
Serum ferritin, ng/mL (Secondary)	**Baseline**		
	Mean (SD)	81.7 (58.26)	85.9 (55.74)
	Week 16, change from baseline		
	LS mean (SE)	-7.7 (9.23)	162.6 (9.00)
	Difference to placebo (SE)	-	170.3 (12.89)
	p-value	-	<0.001[b]
Serum phosphorus, mg/dL (Secondary)	**Baseline**		
	Mean (SD)	4.12 (0.68)	4.23 (0.91)
	Week 16, change from baseline		
	LS mean (SE)	-0.22 (0.07)	-0.43 (0.06)
	Difference to placebo (SE)	-	-0.21 (0.09)
	p-value	-	0.020[b]

Source: Table 4 Xoanacyl SmPC, section 5.1

TSAT = transferrin saturation
a 2-sided chi-squared test; b mixed model repeated measures method with the terms of treatment, baseline value, week post-baseline, and treatment by week post-baseline interactions

A sensitivity analysis (Randomised Period) for the secondary endpoints using an ANCOVA model based on LOCF methodology for the ITT Population was performed. For change from baseline in Hgb, TSAT and ferritin, the sensitivity analysis was largely in line with the primary analysis. For change from baseline in serum phosphorous, the difference between the treatment arms were no longer statistically significant using the sensitivity analysis (Table 15). Furthermore, it is questioned whether a mean decrease with 0.43 mg/dL from 4.18 mg/dL in serum phosphorous is clinically relevant. Notwithstanding, the primary objective for Study 306 was iron deficiency anaemia. The study is considered as a supportive study for hyperphosphataemia. Dose adjustments were primarily based on Hgb parameters and the phosphorous eligibility criterium (serum phosphorous ≥3.5 mg/dL [1.13 mmol/L]) seems primarily intended to mitigate the risk of hypophosphataemia. The weaker effect on serum phosphate in the study is therefore not pursued.

Table 15: Sensitivity analysis of change in serum phosphorus (mg/dL) from baseline over time during randomised period based on LOCF analysis - ITT Population

Parameter		Placebo (N=115)	Xoanacyl (N=117)
Serum phosphorus, mg/dL (Sensitivity analysis)	**Baseline**		
	Mean (SD)	4.12 (0.68)	4.23 (0.91)
	Week 16, change from baseline		
	LS mean (SE)	-0.16 (0.07)	-0.33 (0.07)
	Difference to placebo (SE)	-	-0.17 (0.10)
	p-value	-	0.086

(Compiled by Assessor from CSR Study 306, table 14.2.6.3)

CKD frequently leads to increased levels of hepcidin. Hepcidin is a key regulator of the entry of iron into the circulation in mammals. High levels of hepcidin in the circulation decreases serum iron by iron trapping within macrophages and liver cells, and by decreased gut iron absorption, in turn leading to both absolute and functional iron deficiency. This is at least a part of the explanation to why oral iron supplementation is often considered insufficient in CKD-subjects with iron deficiency anaemia. Upon request, the Applicant has presented a discussion on the potential role of hepcidin for the outcome of Studies 204 and 306. The Applicant points out that the probability of a reduced response to Xoanacyl in the NDD-population due to hepcidin is low, since both transferrin and ferritin increased by treatment.

Study 304

Primary endpoint

The outcome of the primary outcome in the non-EU area is presented in Table 16.

Table 16: Primary endpoint in Study 304 (Serum Phosphate change from baseline from week 52-baseline to Week 56) (ANCOVA) (placebo-controlled period)

Parameter		Placebo (N=91)	Xoanacyl (N=91)
Serum Phosphorus (mg/dL) (non-EU primary)	**Week 52**		
	Mean (SD)	5.44 (1.459)	5.12 (1.189)
	Week 56, change Week 52		
	LS mean (SE)	1.79 (1.767)	-0.24 (1.255)
	LS difference to placebo (SE)	-	-2.18 (0.21)
	p-value	-	<0.001[a]

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).
A sensitivity analysis using MMRM model with terms for treatment group, baseline value, weeks post-baseline, and treatment by weeks post-baseline interaction was consistent with the primary analysis (LS mean [KRX-0502] – LS mean [placebo], -2.07; p<0.0001).

The primary efficacy analysis as requested by the EMA was a non-inferiority analysis at Week 12 of the change from Study-baseline in serum phosphorus comparing Xoanacyl to sevelamer carbonate as single agent, using ANCOVA and LOCF for missing data (Table 17). As supportive data, additional non-inferiority analyses were conducted i) to compare Xoanacyl to the combined active control group for the change in serum phosphorus from baseline to Week 12, and ii) to analyse the change from baseline to Week 12 in calcium x phosphorus product and serum calcium using the same two models (comparing Xoanacyl with sevelamer carbonate and with the combined active control group).

In order to test non-inferiority of Xoanacyl to sevelamer carbonate and to the combined (all) active control group, the ratio of the geometric mean of the experimental treatment effect on serum phosphorus (Week 12 Xoanacyl / Baseline Xoanacyl) (and phosphorus x Ca product and serum calcium) to the geometric mean of the control effect (Week 12 control / Baseline control) on the relevant parameters (serum phosphorus or phosphorus x calcium product or serum Calcium) was estimated.

Non-inferiority was claimed if the upper bound of the 2-sided 95% confidence interval for this ratio lay below 1.2.

Table 17: EU primary endpoint (serum P [mg/dL] change from baseline to week 12) (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).

Non-inferiority vs sevelamer and vs active control for phosphorus x calcium product or serum calcium with ANCOVA and MMRM were in line with the primary analyses (results not presented).

Secondary endpoints

Table 18: Summary of results from secondary endpoints in Study 304 (active-controlled period)

Parameter		Active control (N=146)	Xoanacyl (N=281)
Serum ferritin, ng/mL	**Baseline**		
	Mean (SD)	609.50 (307.69)	592.80 (292.86)
	Week 52, change from baseline		
	LS mean (SE)	26.13 (34.28)	300.04 (25.22)
	LS difference to Active control (SE)	-	273.92 (42.57)
	p-value	-	<0.001[a]
Serum TSAT, %	**Baseline**		
	Mean (SD)	30.8 (11.57)	31.3 (11.21)
	Week 52, change from baseline		
	LS mean (SE)	-1.25 (1.27)	8.07 (0.94)
	LS difference to Active control (SE)	-	9.33 (1.58)
	p-value	-	<0.001[a]

IV iron administration, mg/day	Median daily intake over 52 weeks	3.83	1.87
	p-value	-	<0.0001[b]
IV ESA administration, units/day	Median daily intake over 52 weeks	993.46	755.80
	p-value	-	0.0473[b]

Source: Table 5 Xoanacyl SmPC, section 5.1

a ANCOVA model with treatment as the fixed effect and Study-baseline as the covariate; b 2-sided Wilcoxon Rank Sum Test

The primary analyses for ferritin and TSAT were based via an ANCOVA model with treatment as the fixed effect and Study-baseline as the covariate. Sensitivity analyses created via MMRM model with terms for treatment group, baseline value, weeks post-baseline, and treatment by weeks post-baseline interaction were consistent with the primary analyses (results not presented).

In Study 304, mean Hgb was a post-hoc endpoint (Table 19).

Table 19: Summary of mean Hgb endpoint, g/dL for Xoanacyl (ex AVA1014) (truncated by assessor)

	Study 304 (DD)	
	AVA1014 (N=281)	**Active Control (N=146)**
Baseline, mean (SD)	11.61 (1.24)	11.71 (1.26)
Change from baseline, LS mean (SE) [a]	-0.22 (0.08)	-0.52 (0.11)
Difference (SE)	0.30 (0.14)	-
p-value [b]	0.0340	-

ANCOVA = Analysis of Covariance; CSR = Clinical Study Report; DD = Dialysis-dependent; LS = Least Squares; N = Number of subjects in the treatment group; SD = Standard Deviation; SE = Standard Error.

Source: Study 304 CSR Ad hoc Table 14.2.27.1.
[a] Change from Baseline to 52 weeks.
[b] ANCOVA model with treatment as fixed effect and baseline value as covariate

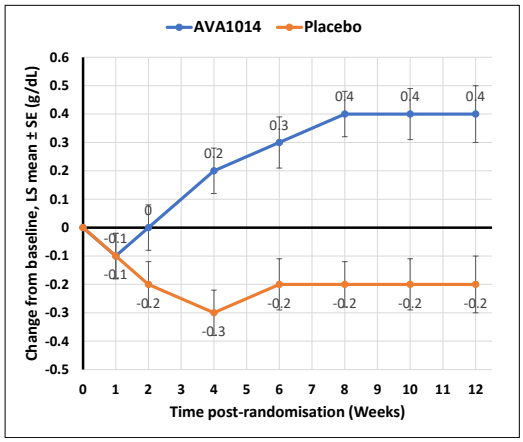
In the DD population, the mean increase in Hgb was very modest at Week 12, and there was a decrease in Hgb over time up to Week 52.

Ancillary analyses

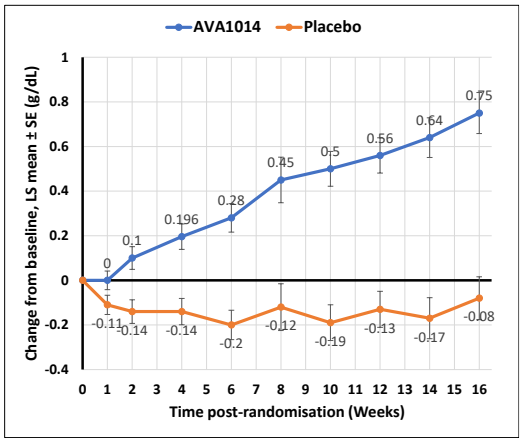
A comparison between change from baseline over time in Hgb in the three pivotal studies is presented in Figure 6.

Figure 6: Change from baseline in Hgb over time in Study 204, Study 306, and Study 304 for Xoanacyl (ex AVA1014)

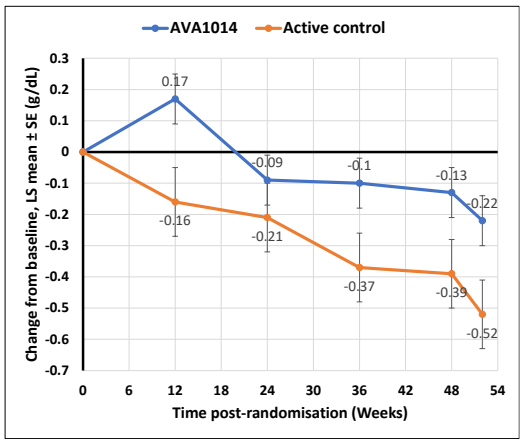
a) Study 204



b) Study 306



c) Study 304



2.5.5.3. Summary of main efficacy results

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 20: Summary of efficacy for trial KRX-0502-204

Title: A Phase 2 Study of KRX-0502 (Ferric Citrate) in Managing Serum Phosphorous and Iron Deficiency in Anemic Subjects with Stage III to V Chronic Kidney Disease Not on Dialysis Note KRX-502 (ferric citrate) is synonymous with Xoanacyl and referred to as such in rest of the table		
Study identifier	KRX-0502-204 (referred to as **Study 204**)	
Design	Multicentre, randomised, double-blind, placebo-controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks 2-week washout from phosphate binder, if applicable not applicable

Hypothesis	Superiority of Xoanacyl to placebo in change from baseline to Week 12 in transferrin saturation (TSAT) and serum phosphorous		
Treatments groups	Xoanacyl 1 g tablets (Xoanacyl)		Starting dose 3 tablets/day (3 g) divided TID with meals and then titrated as needed with maximum of 12 tablets/day (12 g), treatment for 12 weeks duration. 75 subjects randomised / 75 subjects treated.
	Placebo		Starting dose 3 tablets/day divided TID with meals and then titrated with maximum of 12 tablets/day, treatment for 12 weeks duration. 74 subjects randomised / 73 subjects treated.
Endpoints and definitions	Co-primary endpoint	Transferrin saturation (TSAT)	Change from Baseline to Week 12 in TSAT (%)
	Co-primary endpoint	Serum phosphorous	Change from Baseline to Week 12 in serum phosphorous (mg/dL)
	Secondary endpoint	Serum ferritin (ferritin)	Change from Baseline to Week 12 in ferritin (ng/mL)
	Secondary endpoint	Haemoglobin (Hgb)	Change from Baseline to Week 12 in Hgb (g/dL)
	Secondary endpoint	Intact fibroblast growth factor 23 (iFGF23)	Change from Baseline to Week 12 in iFGF23 (pg/mL)
	Secondary endpoint	Urinary phosphorous	Change from Baseline to Week 12 in urinary phosphorus (mg/24 hrs)
	Secondary endpoint	Estimated glomerular filtration rate (eGFR)	Change from Baseline to Week 12 in eGFR (mL/min/1.73 m^2)
Database lock	Date of database lock not reported in CSR, however last subject completed 29 Oct 2013		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (all subjects who were randomised, had a Baseline laboratory value, had taken at least one dose of study drug, and had at least one post-baseline laboratory value). Change from Baseline to Week 12 for co-primary endpoints.		
Descriptive statistics and estimate variability	Treatment group	Xoanacyl	Placebo
	Number of subjects	72	69
	TSAT LS mean, % (SE)	10.2 (1.18)	-1.1 (1.20)
	Serum phosphorous LS mean, mg/dL (SE)	-0.7 (0.07)	-0.2 (0.07)
	TSAT, %	Comparison groups	Xoanacyl vs placebo

Effect estimates per comparison		Difference to placebo	11.3
		SE	(1.70)
		P-value (ANCOVA)	<0.001
	Serum phosphorous, mg/dL	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	-0.5
		SE	(0.10)
		P-value (ANCOVA)	<0.001
Notes	Pre-specified primary analyses for the 2 co-primary endpoints used an ANCOVA model with Baseline as a covariate and a fixed effect for treatment. LOCF was used to impute missing values (i.e., post Baseline missing values were imputed with the last non-missing value from previous scheduled visits). To control overall Type I error rate at 5%, a gatekeeping sequential strategy was pre-specified for the 2 co-primary (and 5 secondary endpoints); sequenced in the order of the list provided in endpoint definition section). Each of the comparisons was made at a type I error rate of 5% and significance claimed only if all previous comparisons in the sequence were significant. Both co-primary endpoints were met. Pre-specified sensitivity analyses included MMRM method in which all follow-up observations were utilised (missing values not imputed). The model included terms for treatment group, baseline value, weeks post baseline, and treatment by weeks post-baseline interaction. Both co-primary endpoints were also met with the MMRM analysis.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat as described for primary analysis Change from Baseline to Week 12 for all secondary endpoints		
Descriptive statistics and estimate variability	Treatment group	Xoanacyl	Placebo
	Number of subjects	72	69
	Ferritin LS mean, ng/mL (SE)	73.3 (7.51)	-4.2 (7.67)
	Hgb LS mean, g/dL (SE)	0.4 (0.10)	-0.2 (0.10)
	iFGF23 LS mean, pg/mL (SE)	-108 (36.21)	17.4 (37.10)
	Urinary phosphorous LS mean, mg/24 hrs (SE)	-269.0 (32.33)	17.5 (33.67)
	eGFR LS mean, mL/min/1.73 m^2 (SE)	-0.3 (0.76)	1.6 (0.79)
Effect estimates per comparison	Ferritin, ng/mL	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	77.5
		SE	(10.83)

		P-value (ANCOVA)	<0.001
	Hgb, g/dL	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	0.6
		SE	(0.14)
		P-value (ANCOVA)	<0.001
	iFGF23, pg/mL	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	-125
		SE	(52.42)
		P-value (ANCOVA)	0.017
	Urinary phosphorous, mg/24hrs	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	-287.0
		SE	(47.15)
		P-value (ANCOVA)	<0.001
	eGFR, mL/min/1.73 m^2	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	-1.9
		SE	(1.11)
		P-value (ANCOVA)	0.079
Notes	The pre-specified analyses with ANCOVA, hierarchical testing strategy, and sensitivity analysis using MMRM were as described for primary analysis. All secondary endpoints were met, except eGFR, which was the final endpoint in the hierarchical testing sequence.		
Analysis description	**Other analysis**		
	Other endpoints also showed differentiation of Xoanacyl from placebo, favouring Xoanacyl were change from baseline to week 12 in serum calcium x phosphorous product, serum CO_2/bicarbonate, UIBC, TIBC, serum iron, Haematocrit, and C-terminal FGF23. The difference in change from baseline to week 12 in iPTH did not reach statistical significance (p=0.056).		

Table 21: Summary of efficacy for trial KRX-0502-306

Title: A Phase 3 Study of KRX-0502 (Ferric Citrate) for the Treatment of Iron Deficiency Anemia in Subjects with Non-Dialysis Dependent Chronic Kidney Disease. Note KRX-502 (ferric citrate) is synonymous with Xoanacyl and referred to as such in rest of the table		
Study identifier	KRX-0502-306 (referred to as **Study 306**)	
Design	Multicentre, randomised, double-blind, placebo-controlled with open label extension phase	
	Duration of main phase:	16 weeks Randomised Period
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	8 weeks Extension Period
Hypothesis	Superiority of Xoanacyl to placebo in percentage of haemoglobin responders	

Treatment groups (Randomised Period)	Xoanacyl 1 g tablets (Xoanacyl)		Starting dose 3 tablets/day (3 g) divided TID with meals and then titrated as needed with maximum of 12 tablets/day (12 g), treatment for 16 weeks duration in Randomised Period. 117 subjects randomised / 117 subjects treated in Randomised Period.
	Placebo		Starting dose 3 tablets/day divided TID with meals and then titrated with maximum of 12 tablets/day, treatment for 12 weeks duration, 117 subjects randomised / 116 subjects treated in Randomised Period.
Treatment Groups (Extension Period)	Xoanacyl 1 g tablets (Xoanacyl)		All subjects start at 3 g/day (regardless of prior dose) which can then be titrated. 167 subjects treated in Extension Period (86 subjects from prior Xoanacyl arm, 81 subjects from prior placebo arm)
Endpoints and definitions	Primary endpoint	Haemoglobin responders (Hgb responders)	Proportion of subjects with haemoglobin of ≥1.0 g/dL at any time in Randomised Period (% of subjects)
	Secondary endpoint	Haemoglobin (Hgb)	Change from Baseline to Week 16 in Hgb (g/dL)
	Secondary endpoint	Transferrin saturation (TSAT)	Change from Baseline to Week 16 in TSAT (%)
	Secondary endpoint	Serum ferritin (ferritin)	Change from Baseline to Week 16 in ferritin (ng/mL)
	Secondary endpoint	Sustained Hgb responders	Proportion of subjects with a change ≥0.75 g/dL over any 4-week time period in the Randomised Period, provided subject also achieved ≥1.0 g/dL during this 4-week period (% of subjects)
	Secondary endpoint	Serum phosphorous	Change from Baseline to Week 16 in serum phosphorous (mg/dL)
Database lock	Date of database lock not reported in CSR, but last subject completed the study on 15 Jan 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (all subjects who were randomised, had a Baseline laboratory value, had taken at least one dose of study drug, and had at least one post-baseline laboratory value). Over the 16-week Randomised Period		
Descriptive statistics and estimate variability	Treatment group	Xoanacyl	Placebo
	Number of subjects	117	115
	Hgb responders, no. subjects (%)	61 (52.1)	22 (19.1)
Effect estimates per comparison	Hgb responders, % of subjects	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	33.0

		95% CI	(21.4, 44.6)
		P-value (2-sided chi-square test)	<0.001
Notes	For the pre-specified primary analyses, subjects who discontinued the study before the end of the Randomised Period and before achieving an increase from Baseline in Hgb of ≥1.0 g/dL were considered non-responders. The primary endpoint and 5 secondary endpoints were evaluated according to a pre-specified hierarchy to control Type I error. Each of the comparisons was made at a type I error rate of 5% and significance claimed only if all previous comparisons in the sequence were significant. The primary endpoint was met.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat as described for primary analysis. Change from Baseline to Week 16, except Sustained Hgb responders which was over any 4-week period in the 16-week Randomised Period		
Descriptive statistics and estimate variability	Treatment group	Xoanacyl	Placebo
	Number of subjects	117	115
	Hgb LS mean, g/dL (SE)	0.75 (0.09)	-0.08 (0.10)
	TSAT LS mean, % (SE)	17.8 (1.37)	-0.6 (1.37)
	Ferritin LS mean, ng/mL (SE)	162.6 (9.00)	-7.7 (9.23)
	Sustained Hgb responder, no. subjects (%)	57 (48.7)	17 (14.8)
	Serum phosphorous LS mean, mg/dL (SE)	-0.43 (0.06)	-0.22 (0.07)
Effect estimates per comparison	Hgb, g/dL	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	0.84
		SE	(0.13)
		P-value (MMRM)	<0.001
	TSAT, %	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	18.4
		SE	(1.94)
		P-value (MMRM)	<0.001
	Ferritin, ng/mL	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	170.3
		SE	(12.89)
		P-value (MMRM)	<0.001
		Comparison groups	Xoanacyl vs placebo

	Sustained Hgb responders, % of subjects	Difference to placebo	33.9
		95% CI	(22.8, 45.1)
		P-value (2-sided chi-square test)	<0.001
	Serum phosphorous, mg/dL	Comparison groups	Xoanacyl vs placebo
		Difference to placebo	-0.21
		SE	(0.09)
		P-value (MMRM)	0.020
Notes	For all non-proportion-related endpoints, a Mixed Model Repeated Measures (MMRM) with corresponding baseline value as a covariate was fit with treatment, week, and treatment-by-week interaction as fixed effects and subject as a random effect. The MMRM analysis utilised the maximum likelihood estimation method. The proportion of sustained responders was analysed as described for primary endpoint. All secondary endpoints were met per the pre-specified hierarchical testing strategy.		
Analysis description	**Other analysis**		
	Other endpoints that also showed significant differentiation of Xoanacyl from placebo in the Randomised Period were change from baseline to Week 16 in serum CO_2/bicarbonate, UIBC, TIBC, serum iron, HCT, iPTH, C-terminal FGF23, intact FGF23, proportion of subjects with Hgb ≥0.75 g/dL in last 4 weeks, and time to first Hgb increase ≥1.0 g/dL. No significant difference between the groups was seen for serum calcium or eGFR during the 16-week Randomised Period. During the Extension Period, patients who switched from placebo to Xoanacyl had increases in iron-related parameters and decrease in serum phosphorus. In the subjects who remained on Xoanacyl, continued benefit was observed with initial changes consistent with a decrease in mean dose that was observed on entering the Extension Period when dose re-set to 3 g/day.		

Table 22: Summary of efficacy for trial KRX-0502-304

Title: A Three=Period, 58-Week Safety and Efficacy Trial of KRX-0502 (Ferric Citrate) in Patients with End-Stage Renal Kidney Disease (ESRD) on Dialysis. Note KRX-502 (ferric citrate) is synonymous with Xoanacyl and referred to as such in rest of the table		
Study identifier	KRX-0502-304 (referred to as Study 304)	
Design	Multicentre, randomised, active controlled period with randomised placebo-controlled period	
	Duration of main phases:	52 weeks active-controlled phase
	Duration of Run-in phase:	4 weeks placebo-controlled phase, for subjects treated with Xoanacyl in active-controlled period 2-week washout from current phosphate binder
	Duration of Extension phase:	Not applicable (separate extension study)
Hypothesis (non-EU)	Superiority of Xoanacyl to placebo in change in serum phosphorus during placebo-controlled period.	
Hypothesis (EU)	Non-inferiority of Xoanacyl to sevelamer carbonate in change in serum phosphorous from baseline to Week 12 in active-controlled phase	

Treatment groups Active-Controlled Phase	Xoanacyl 1 g tablets (Xoanacyl)		Starting dose 6 tablets/day (6 g) divided TID with meals and then titrated as needed with maximum of 12 tablets/day (12 g), treatment for 52 weeks 292 subjects randomised / 289 subjects treated.
	Active control Calcium acetate or sevelamer carbonate, or any combination of calcium acetate and sevelamer carbonate		Starting doses were based on the last dose that was administered prior to the start of the washout (if the subject remained on the same phosphate binder) or if the subject's phosphate binder regimen was altered at the discretion of the Investigator, guided by the package insert. 149 subjects randomised / 149 subjects treated.
Treatment groups Placebo-Controlled Phase	Xoanacyl1 g tablets (Xoanacyl)		Subjects continued on same Xoanacyl dose as at end of active-controlled phase; treatment for 4 weeks. 96 subjects randomised / 95 subjects treated.
	Placebo		Subjects received matched placebo; treatment for 4 weeks. 96 subjects randomised / 95 subjects treated.
Endpoints and definitions	Primary endpoint (non-EU)	Serum phosphorous	Change in serum phosphorus from Week-52-Baseline (end of active-controlled phase) to Week 56 (end of placebo-controlled phase) (mg/dL)
	Primary endpoint (EU)	Serum phosphorous Week 12	Change from Baseline to Week 12 in serum phosphorus for subjects receiving sevelamer carbonate or Xoanacyl (mg/dL)
	Secondary endpoint	Serum ferritin (ferritin)	Change from Baseline to Week 52 in ferritin (ng/mL)
	Secondary endpoint	Transferrin saturation (TSAT)	Change from Baseline to Week 52 in TSAT (%)
	Secondary endpoint	IV iron use (IV iron)	Cumulative use of IV iron over 52 weeks (median IV intake, mg/day)
	Secondary endpoint	IV erythropoietin stimulating agent use (IV ESA)	Cumulative use of IV ESA over 52 weeks (median IV intake, units/day)
Database lock	Date of database lock not reported in CSR, but last subject completed the study on 07 Nov 2012		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis (non-EU)**		

Analysis population and time point description	Full Analysis (FA) population which consists of all randomised subjects who received at least 1 dose of study drug and a baseline serum phosphorous value, had taken at least one dose of study drug, and had at least one post Baseline serum phosphorus value. Placebo-controlled Period: Change from Baseline of placebo-controlled period (Week 52) to Week 56.			
Descriptive statistics and estimate variability	Treatment group	Xoanacyl	Active Control	Placebo
	Number of subjects	91	NA	91
	Serum phosphorous mean change, mg/dL (SD)	-0.24 (1.255)	NA	1.79 (1.767)
Effect estimates per comparison	Serum phosphorous, mg/dL	Comparison groups	Xoanacyl vs placebo	
		LS mean difference to placebo	-2.18	
		SE	(0.21)	
		P-value (ANCOVA)	<0.0001	
Notes	For the pre-specified primary analyses, an ANCOVA model with imputation of missing values with LOCF, treatment as the fixed class effect and Week 52-baseline as the covariate. The primary endpoint and 4 secondary endpoints were evaluated according to a pre-specified hierarchy to control Type I error. Each of the comparisons was made at a type I error rate of 5% and significance claimed only if all previous comparisons in the sequence were significant. The primary endpoint was met. A pre-specified sensitivity analysis using a Mixed Model Repeated Measures (MMRM) was also performed on the primary endpoint with no imputation of missing values and terms for treatment group, baseline value, weeks post-baseline, and treatment by weeks post-baseline interaction. The primary endpoint was also met with the MMRM analysis.			
	Primary Analysis (EU)			
Analysis population and time point description	Full Analysis population as described for non-EU primary analysis, except only sevelamer carbonate as single agent for control group. Active-controlled Period: Change from Baseline to Week 12 for serum phosphorous [a].			
Descriptive statistics and estimate variability	Treatment group	Xoanacyl	Active Control (sevelamer carbonate)	Placebo
	Number of subjects	281	78	NA
	Serum phosphorous Week 12 mean change, mg/dL (SD)	-2.02 (1.998)	-2.21 (2.175)	NA
Effect estimates per comparison	Serum phosphorous Week 12	Comparison groups	Xoanacyl vs sevelamer carbonate	

		LS mean difference to sevelamer carbonate	0.14	
		SE	(0.19)	
		P-value (ANCOVA)	0.4733	
Notes	[a] For the NI analysis see subsequent rows. For the pre-specified analysis an ANCOVA model with imputation of missing values with LOCF, treatment as the fixed class effect and Study-baseline as the covariate was used. MMRM sensitivity analysis also performed. No significant difference observed between Xoanacyl and sevelamer carbonate groups (or to overall active control group); NI was tested separately (see next rows).			
Analysis population and time point description (for NI)	Full Analysis population as described for non-EU primary analysis, except only sevelamer carbonate as single agent for control group. Active-controlled Period: Non-inferiority (NI) of change from Baseline to Week 12 for serum phosphorous [a].			
Descriptive statistics and estimate variability (for NI)	Treatment group	Xoanacyl	Active Control (sevelamer carbonate)	Placebo
	Number of subjects	281	78	NA
	Serum phosphorous Week 12 GLSM ratio (95% CI) [a]	0.715 (0.69, 0.74)	0.695 (0.65, 0.74)	NA
Effect estimates per comparison	Serum phosphorous Week 12 GLSM treatment ratio [a]	Comparison groups	Xoanacyl vs sevelamer carbonate	
		Treatment ratio of GLSM [a]	1.029	
		95% CI (ANCOVA)	(0.959, 1.104)	
		P-value	NA	

Notes	GLSM = geometric least squares mean [a] For the purposes of the non-inferiority (NI) analysis, data were transformed on the logarithmic scale to normalise distribution of the results. Consequently, all data are expressed as geometric means (i.e., re-exponentiated means of logarithms), and changes in serum phosphorous between Baseline and Week 12 are expressed as GLSM ratios (serum phosphorous at Week 12 / serum phosphorous at Baseline). To test NI of Xoanacyl to sevelamer carbonate, the ratio of the GLSM ratio of the Xoanacyl treatment effect (Week 12 Xoanacyl / Baseline Xoanacyl) on serum phosphorous to the GLSM ratio of the sevelamer bicarbonate effect (Week 12 sevelamer / Baseline sevelamer) on serum phosphorous was estimated. If the 95% confidence interval (CI) for this treatment ratio lay completely below 1.2 (i.e., the Week 12 change in serum phosphorous relative to Baseline by Xoanacyl, was within 20% of that of sevelamer carbonate). Two models were employed for Week 12 serum phosphorous levels: ANCOVA with LOCF to impute missing data, and MMRM as a sensitivity analysis, each adjusted for Baseline serum phosphorous and using treatment as a factor. NI of Xoanacyl to sevelamer carbonate was demonstrated for both models (also to overall active control group).			
Analysis description	**Secondary analysis**			
Analysis population and time point description	Full Analysis population as described for primary analysis. Active-controlled Period: Change from Baseline to Week 52 for ferritin and TSAT; over 52-week period for IV iron and ESA.			
Descriptive statistics and estimate variability	Treatment group	Xoanacyl	Active control	Placebo
	Number of subjects	281	146	NA
	Serum ferritin LS mean, ng/mL (SE)	300.04 (25.22)	26.13 (34.28)	NA
	TSAT LS mean, % (SE)	8.07 (0.94)	-1.25 (1.27)	NA
	IV iron, median daily intake mg/day	1.87	3.83	NA
	IV ESA, median daily intake units/day	755.80	993.46	NA
Effect estimate per comparison	Serum ferritin, ng/mL	Comparison groups	Xoanacyl vs active control	
		Difference to active control	273.92	
		SE	(42.57)	
		P-value (AVCOVA)	<0.0001	
	TSAT, %	Comparison groups	Xoanacyl vs active control	
		Difference to active control	9.33	
		SE	(1.58)	
		P-value (AVCOVA)	<0.0001	
	IV iron, median intake, mg/day	Comparison groups	Xoanacyl vs active control	

		P-value of difference in medians (2-sided Wilcoxon Rank Sum Test)	<0.0001
	IV ESA, median intake, units/day	Comparison groups	Xoanacyl vs active control
		P-value of difference in medians (2-sided Wilcoxon Rank Sum Test)	0.0473
Notes	For pre-specified secondary analyses of ferritin and TSAT, LOCF ANCOVA model with treatment as the fixed effect and Study-baseline as the covariate. MMRM sensitivity analyses were also performed. For IV iron and ESA use, the basic assumptions for ANCOVA were not met so a non-parametric test was used, as permitted by the statistical analysis plan. All secondary endpoints were met per the pre-specified hierarchical testing strategy.		
Analysis description	**Other analysis**		
	Significant differences favouring Xoanacyl versus the active control were also observed for various other iron parameters including changes from Baseline to Week 52 in serum iron, TIBC and Hgb. For serum phosphorous, Xoanacyl compared to the active control phosphate binder did not show significant differences at Week 12 or Week 52 (NI tested versus sevelamer carbonate at Week 12 for EU primary endpoint as described earlier; also tested versus overall control group). No significant difference was observed in the change from Baseline to Week 52 between the Xoanacyl and active comparator arms for other phosphorous-related parameters such as proportion of subjects achieving serum phosphate levels to different thresholds, calcium x phosphorus product and serum calcium.		

2.5.5.4. Clinical studies in special populations

The number of subjects in special populations in the three pivotal studies are summarised in Table 23.

Table 23: Compiled number of subjects in special populations from the 3 pivotal studies (ITT population)

	Controlled Trials (ITT population)	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	800 / 800	NA
Hepatic impairment** patients (Subjects number /total number)	109 / 800	NA
Paediatric patients <18 years (Subjects number /total number)	0 / 800	NA
Age 65-74 (Subjects number /total number)	193 / 800	NA
Age 75-84 (Subjects number /total number)	92 / 800	NA

	Controlled Trials (ITT population)	Non-controlled trials
Age 85+ (Subjects number /total number)	16 / 800	NA

2.5.5.5. In vitro biomarker test for patient selection for efficacy

N/A

2.5.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.5.5.7. Supportive studies

Data from the scientific literature

The Applicant presented an article from the scientific literature (Block et al., 2019) as a key supportive study to bridge data from the NDD- to the DD-population. The study was funded by Keryx Biopharmaceuticals i.e., the Applicant for Fexeric. The Principal Investigator and coinvestigators were however responsible for the design, conduct, and analysis of the study with no input from Keryx Biopharmaceuticals. The article was provided as background information; however, no study report was presented. This hampers the secondary assessment of the study. Anaemia and CKD–related disordered mineral metabolism (including abnormalities in phosphate and fibroblast growth factor 23 [FGF23]) are believed to contribute to adverse outcomes in subjects with advanced CKD. To investigate the effects of fixed-dose ferric citrate coordination complex in such patients, the authors randomly assigned 199 patients with eGFR<20 ml/min per 1.73 m2 2:1 to ferric citrate coordination complex or usual care in a randomised, active-controlled open-label, single-centre study. Patients randomised to usual care could be treated with any medication, including P binders other than FCCC ESAs, red blood cell transfusion, active vitamin D, and oral or intravenous iron were permitted at the discretion of the treating nephrologist. Eligibility criteria included serum phosphorus ≥ 3.0 mg/dL [0.97 mmol/L], Hgb > 8.0 g/dL, TSAT < 55%, and with an anticipated at least 8 weeks before the need for dialysis. Subjects in the Xoanacyl arm started at a dose of 3 g/day which was increased to a fixed dose of 6 g/day after 2 weeks (protocol was subsequently amended to start patients on 6 g/day). Dose titration was only permitted if there was persistently low or high serum phosphorus (<3.0 mg/dL [0.97 mmol/L] or >5 mg/dL [1.61 mmol/L]) or persistently high TSAT (>60%).

The two groups had generally similar baseline characteristics, although diabetes and peripheral vascular disease were more common in the usual-care group. Ferric citrate coordination complex significantly increased Hgb, transferrin saturation, and serum ferritin, and it significantly reduced serum phosphate and intact FGF23 (P<0.001 for all). Of the 133 patients randomised to ferric citrate coordination complex, 31 (23%) initiated dialysis during the study period, as did 32 of 66 (48%) patients randomised to usual care (P=0.001). Compared with usual care, ferric citrate coordination complex treatment resulted in significantly fewer annualised hospital admissions, fewer days in hospital, and a lower incidence of the composite end point of death, provision of dialysis, or transplantation (P=0.002).

The authors of the article conclude that treatment with fixed-dose FCCC in patients with eGFR ≤20 ml/min per 1.73 m 2 corrects anaemia (without the routine use of intravenous iron or ESA) and favourably affects parameters of CKD-MBD. Effects of FCCC on death, provision of dialysis, and

hospitalisation suggest that this strategy is safe and potentially beneficial. These findings strongly support the conduct of an event-driven, multicentre, placebo-controlled RCT examining the effects of ferric citrate coordination complex on death, the provision of dialysis, or kidney transplantation in patients with advanced CKD.

Study 402

Long-term efficacy and safety of Xoanacyl in the NDD population was assessed in Study 402 during a 24—week titration period and an observation period of an additional 24 weeks. Doses were titrated from a starting dose of either 3 or 4 tablets to maximum 6 tablets of Xoanacyl.

During the titration period, mean Hgb increased from 10.45 to 11.21 g/dL, being stable for the observation period, while ferritin increased over the entire 48 weeks (ferritin 136-283-446 ng/mL for baseline, Week 24 and Week 48, respectively), indicative of increased iron stores. TSAT increased from 17.6% to 24.6% at Week 24 and 27.4% at Week 48.

Mean serum phosphate was within the normal range at baseline (3.9 mg/dL [1.29 mmol/L]) and remained within the normal range at Week 24 (3.7 mg/dL [1.19 mmol/L]) and Week 48 (3.8 mg/dL [1.23 mmol/L]).

In summary, the results from Study 402 indicate a consistent effect on over time on Hgb and phosphate up to 48 weeks. Of note, mean baseline serum phosphate was within the normal range at baseline. Ferritin levels increased during the entire 48-week-period, indicating that monitoring of serum ferritin should continue during treatment.

2.5.6. Discussion on clinical efficacy

Design and conduct of the clinical studies

Study design

The MAA is based on three pivotal studies: Study 204 and Study 306 in subjects with non-dialysis dependent CKD (NDD CKD), and Study 304 in subjects with dialysis dependent CKD (DD CKD). All studies were conducted in a Western but non-EU population (mainly the US). The Applicant's justification for the study population being relevant to the EU population is acknowledged.

- Study 204 was a 12 -week Phase 2, multicentre, randomised, double-blind, placebo-controlled trial.
- Study 306 was a Phase 3, multicentre, randomised study with two Study Periods: a 16-week double-blind, placebo-controlled randomised period and an 8-week, single-arm, open-label extension period.
- Study 304 was a Phase 3, multicentre, randomised, open-label study with a 52-week active-controlled period and a 4-week placebo-controlled period. The EU-primary endpoint and the secondary endpoints were evaluated at Week 52, whereas the US primary endpoint was evaluated Week 52-56.

The studies were completed 8-12 years ago. There have not been any major changes in the therapeutic landscape for treatment of iron deficiency anaemia and hyperphosphataemia in the CKD population during the last 10 years. The phosphate binders used as active control in Study 304, calcium acetate and sevelamer, are still widely used. During the last years, two Hypoxia-inducible factor prolyl hydroxylase Inhibitors (HIF-PHI) have been approved in EU. These products however stimulate erythropoiesis rather than increase iron stores and do not impact on the relevance of the studies in this application.

As discussed below, the design of Study 304 is evidently focussed on evaluating the effect of FCCC on hyperphosphataemia. Study 204 is designed with a dual focus. Study 306, which was not part of the MAA for Fexeric, is clearly focussed on iron deficiency. For the NDD-population, both mechanisms of action are therefore represented in the pivotal studies, whereas there is no pivotal study in the DD-population with a dedicated focus on iron deficiency.

The choice to use placebo as comparator in study 204 and during the 16-week randomised period in study 306 to establish the absolute effect of Xoanacyl is followed and agreed.
In Study 304, the randomised period was longer and the study population, being a DD-population, had more pronounced hyperphosphataemia. It is agreed with the Applicant that it would not have been possible to leave the subjects in the comparator arm without phosphate lowering therapy during the treatment period. Therefore, the study was active-controlled (calcium acetate or sevelamer carbonate or any combination of calcium acetate and sevelamer carbonate at the discretion of the Investigator). Treatment with calcium acetate and/or sevelamer in CKD subjects with hyperphosphataemia is standard of care in EU and deemed adequate as active comparator(s). However, since calcium acetate and sevelamer have no known effect on iron stores and blood formation, the study was active-controlled only for serum phosphate and other CKD-MBD related endpoints.

Study population

All studies recruited adult CKD subjects with high baseline serum phosphate and signs of iron deficiency anaemia with eGFR < 60 mL/min (Study 204 and Study 306) or with dialysis (Study 304).

The eligibility ranges for iron deficiency parameters were serum ferritin ≤300 ng/mL, TSAT ≤30% and Hgb >9.0 to <12.0 g/dL in Study 204. In Study 306 the ranges were serum ferritin ≤200 ng/mL, TSAT ≤25% and Hgb ≥9.0 to ≤11.5 g/dL, and in Study 304 serum ferritin <1000 ng/mL, TSAT <50% and no requirement of Hgb below the lower limit of normal.

The eligibility criteria should be seen in light of definitions and treatment targets for iron deficiency anaemia in the CKD population.
In clinical practice, iron deficiency is normally evaluated by transferrin saturation (TSAT) and ferritin levels. The normal range for TSAT and ferritin varies widely among sources, but serum ferritin values <30 ng/mL indicate severe iron deficiency and are highly predictive of absent iron stores in bone marrow. In the NDD-population, TSAT <20% and ferritin <100 ng/dL (<200 ng/dL for the DD-population) has been proposed as arbitrary limits for probable absolute iron deficiency and TSAT <20% and ferritin ≥100 ng/dL (DD: >200 ng/mL) as limits for probable functional iron deficiency.
In the 2012 KDIGO anaemia guideline, a 1- to 3-month trial of IV iron (or in CKD NDD patients alternatively of oral iron therapy) is suggested to adult anaemic CKD subjects with TSAT is ≤30% and ferritin is ≤500 ng/ml, if an increase in Hgb without starting ESA treatment is desired, and the subject is not on iron or ESA therapy. There are no fixed target levels for TSAT and ferritin with iron treatment. However, it is often recommended to discontinue iron treatment at ferritin ≥ 800 ng/mL to mitigate the risks of iron overload. The KDIGO 2012 anaemia guideline suggests that ESAs should not be used to maintain Hb concentration above 11.5 g/dl in adult patients with CKD as the benefit/risk ration is questioned. There is also a strong recommendation not to aim for Hgb increases to concentrations ≥13 g/dl based on the interpretation of the combined results of major RCTs showing more harm than benefit with higher Hgb targets, including increased risks for stroke, hypertension, and vascular access thrombosis (in haemodialysis patients).
In the WHO classification of anaemia, moderate anaemia can be recognised in subjects with Hgb levels 8-10.9 g/dL. The Applicant clarified that the study population was selected to reflect the intended target population. The chosen Hgb cut-off of 9 g/dL was also related to a higher risk of a need of ESA therapy and IV iron which would affect interpretation of the study results.

The normal range for serum phosphate in adults varies between sources but is commonly given as 2.5 or 3.0 to 4.5 mg/dL (0.81 or 0.97 -1.45 mmol/L).
The eligibility range for phosphate was ≥4.0 -<6.0 mg/dL [≥1.29 - 1.94 mmol/L] in subjects previously not treated with phosphate binders or after two weeks of washout in Study 204, ≥3.5 mg/dL [1.13 mmol/L] in Study 306, and ≥2.5 - ≤8.0 mg/dL [0.81 - 2.58 mmol/L] at screening in Study 304. To be eligible for randomisation, serum phosphorus had to be ≥6.0 mg/dL [1.94 mmol/L] at the end of the washout period of Study 304.
A limitation with Study 204 is that the eligibility criteria included an upper level of serum phosphate, thereby excluding the subjects with the highest need for phosphate binders. In study 306, there was no upper limit in serum phosphate for study inclusion. Still, mean baseline phosphate in Study 306 was lower than in Study 204. Nevertheless, a robust effect on serum phosphate in Study 304, representing a study population with marked hyperphosphataemia, compared to placebo and to other phosphate binders was demonstrated. There are no mechanistic or physiological reasons that Xoanacyl would not have the same effect on high phosphate in the NDD as in the DD population. Therefore, the effect of Xoanacyl in more pronounced hyperphosphataemia is considered possible to extrapolate from the DD- to the NDD-population.

According to the endpoints of the studies, Study 304 and to some extent Study 204 were mainly designed to evaluate the effect on hyperphosphataemia, whereas Study 306 was mainly designed to study the effect on iron deficiency. This is reflected in the eligibility criteria. For example, the eligibility criterium for phosphate in Study 306 is well within the normal range and better suited to avoid hypophosphataemia with iron treatment than to treat hyperphosphataemia. Likewise, the iron deficiency inclusion criteria for Study 304 seem more adequate to mitigate the risk for iron overload than to identify a study population with iron deficiency anaemia.

In summary, the eligibility criteria in Study 204 and Study 306 in combination are adequate to assess iron deficiency (anaemia) in NDD subjects with high phosphate, whereas the eligibility criteria in Study 304 are not considered fully adequate to create a study population suitable for assessment of the effect of Xoanacyl on iron deficiency anaemia. This is further discussed below.

Dosing

In the NDD studies, the starting dose of Xoanacyl was 3 tablets per day which is also the recommended starting dose in the SmPC. The starting dose in Study 304 was 6 tablets daily. The recommended starting dose in the SmPC for the DD-population is however 3-6 tablets per day. All subjects included in Study 304 (starting dose 6 g) were on stable treatment with other phosphate binders. The Applicant clarified that the lower dose could be useful when starting treatment in DD-subjects naïve to phosphate binders and in subjects already on treatment with Xoanacyl starting dialysis. The starting dose will be up- and down-titrated pending on phosphate and ferritin levels according to recommendations in SmPC section 4.2, and therefore, this rationale for the lower starting dose in the study is accepted.

In Study 204 and Study 304, the Xoanacyl dose was adjusted to reach a serum phosphate target level, whereas in Study 306 the dose adjustments were based on Hgb. The advantage with a dual effect of Xoanacyl, simultaneously addressing two common but unrelated conditions in CKD subjects, is acknowledged. However, this mechanism of action may also limit the use of the product. The Applicant did not systematically gather information on dose adjustments, treatment holds, and treatment discontinuations prompted by the effect on one condition leading to insufficient treatment of the other system. It is expected that such conflicts will occasionally occur in clinical practice. This is however managed by SmPC-wordings.

In the DD study 304, IV iron and ESA was allowed which complicates dosing of all three compounds. Due to an increased cardiovascular risk with normalising Hgb with the use ESA, the target level for Hgb

under ESA treatment is typically around 10.5-11.5 g/dL. There was no guidance on adjustment of dosing of Xoanacyl based on Hgb levels in Study 304 (DD-population). Adjustments of IV iron and erythropoiesis stimulating agents (ESA) were left to the discretion of the investigators. IV iron was not recommended if the serum ferritin was >1000 ng/mL or the TSAT was >30%.

Endpoints

Change from baseline in serum phosphate was a co-primary endpoint in Study 204 and a secondary endpoint (last in hierarchy) in Study 306. In Study 304, there are two alternative primary endpoints related to phosphate, one for the EU (change in serum phosphate from baseline to Week 12; non-inferiority versus active control) and one for the non-EU area (change in serum phosphorus levels versus placebo from Week 52 to Week 56).
Change from baseline in serum phosphate has earlier been widely accepted as primary endpoint in trials with products indicated for treatment of hyperphosphataemia.

Iron stores were evaluated by change from baseline in serum ferritin and TSAT, which is considered adequate. TSAT was a (co)-primary endpoint in study 204 and a secondary endpoint in Study 306 and 304. Ferritin was a secondary endpoint in all three studies.
Anaemia was evaluated by change from baseline in Hgb, which was a secondary endpoint in Study 204 and Study 306.

The primary endpoint of Study 306 was the proportion of subjects achieving an increase in Hgb of ≥1.0 g/dL at any point between baseline and the end of the randomised period. Considering the margin of error for the measurement, impact of dehydration on Hgb values, etc., the definition of an increase in Hgb of ≥1.0 g/dL at any point between baseline and Week 16 as response seems to be quite blunt. Nonetheless, the totality of data including the responder analysis and change from baseline Hgb at Week 16 (secondary endpoint) is considered adequate for evaluating an effect on Hgb in this study. This issue is therefore not pursued.

Statistical considerations

The statistical analysis plan for each of the studies 204, 306 and 304 shared a number of features.

To be included in the primary efficacy analysis population, the following requirements applied: were randomised, had a baseline laboratory value, had taken at least one dose of study drug, and had at least one post-baseline laboratory value. The definition of the ITT (study 204 and 306) and FAS (study 304) analysis set was not fully endorsed, especially regarding the requirement of providing post-baseline data.

For continuous primary and secondary endpoints, the predefined sensitivity analyses either relied on MMRM (MAR) or ANCOVA (LOCF). The sensitivity analyses performed were questioned in that they may not have been sufficiently conservative (see also points below).

All the studies used the same approach for defining a multiple testing procedure. The gatekeeping sequential strategy chosen is agreed to protect the overall type I error.

Study 204

The definition of the ITT population implied that 4.0% (3/75) and 6.8% (5/74) of the subjects in the KRX-0502 and the placebo arm respectively was excluded from the primary analysis.

Primary missing data handling using LOCF is not supported. The number of subjects who terminated the study early was 14/75 (18.7%) in the Xoanacyl arm and 24/74 (32.4%) in the placebo arm. The sensitivity analyses were not considered sufficiently conservative to challenge robustness in that they relied on MMRM (MAR). However, requested additional analyses of the primary and multiplicity corrected secondary endpoints measuring iron related outcomes confirmed that the primary analysis

was robust. Regarding concerns about the amendment half-way into the study which implied that the primary endpoint ranked the highest became a secondary endpoint, it was acknowledged that this study should have met its primary objective(s) based also on the original analysis plan. (See also below Study conduct).

Study 306

Regarding that the definition of the ITT population is not according to the preferred: "only" two subjects from the placebo arm were excluded from the ITT analysis.

The proportion of randomised subjects not completing the randomised 16-week period was 31/117 (26.5%) subjects in the Xoanacyl arm and 35/117 (29.2%) in the placebo arm. The most common reason in both arms was an AE.

The primary endpoint was a responder analysis with missing data imputed as treatment failure, i.e., non-responders. This was accepted.

For continuous secondary endpoints included in the multiple testing procedure, the analysis was by the use of MMRM and the assumption of missing being missing at random (MAR). The only sensitivity analyses performed relied on an ANCOVA and the use of last-observation-carried-forward (LOCF). Therefore, additional sensitivity analyses based on MMRM although assuming MNAR was requested. These confirmed that the primary analysis of each endpoint concerned was statistically robust.

A total of 450 subjects expected to be screened turned out to be a total of 645 screened subjects. A total of 232 subjects were randomised which was very close to expectations.

Study 304

The "alternate primary endpoint for EMA" was added within a protocol amendment, although had no place in the closed testing procedure.

The primary efficacy analysis as requested by the EMA (as part of MAA of Fexeric EMEA/H/C/003776/0000), was a non-inferiority analysis at Week 12 of the change from study baseline in serum phosphorus comparing KRX-0502 to sevelamer carbonate as single agent.

Study conduct

The number of protocol deviation was high, especially in study 304. In the MAA procedure for Fexeric, the Applicant was asked to justify the absence of impact of these protocol deviations to both efficacy and safety. Although the response is not comprehensive, in particular excluding data from Study 204, the data presented is considered sufficient and the issue is not further pursued.

The fourth protocol amendment in study 204 is dated 01 May 2013, i.e., halfway through the study. In this amendment, serum ferritin was downgraded from the third component of the co-primary endpoint to the first secondary endpoint. At this time point, approximately half of the study population was enrolled, and given the short observation time, a non-negligible part of the study population would have completed the study. Changes in primary endpoint during the course of the study is highly discouraged. It is however reassuring that all data remained blinded until the last subjects had completed the study and that sensitivity analysis showed that the original primary endpoint including ferritin would also have been met in the study. This issue is not further pursued.

The Applicant clarified that seven subjects, three in the placebo arm and four in the Xoanacyl arm, were enrolled in the study despite baseline Hgb outside the revised inclusion criteria of >9.0 and <12.0 g/dL. Of the seven subjects enrolled with Hgb outside the extended eligibility criteria, there were two with a baseline Hgb ≤9.0 g/dL and five with Hgb ≥12.0 g/dL. Both subjects with Hgb ≤9.0 g/dL were

from the placebo arm. Since inclusion was randomised, this is not considered of relevance for the outcome.

The Applicant has not offered any explanation to the enrolment of subjects with baseline Hgb outside the revised inclusion criteria. It is however not expected that the erroneous inclusion of seven subjects (7/149; 4.7%) has affected the outcome. The issue is therefore not further pursued.

The second amendment of Study 304 introduced the option to switch a subject from active control to treatment with KRX-0502 if developing hypercalcemia on either calcium acetate as a single agent or in the combination of calcium acetate and sevelamer carbonate. The Applicant clarified that 245 subjects were enrolled prior to Amendment 2, which constitutes more than 55% of the population randomised into Study 304. The Applicant clarified that the amendment should not be expected to affect the study results since the follow-up was more than a year and titration was based on the serum phosphorus values. In total, four subjects were switched from active control to Xoanacyl. It is not evident how these subjects were handled statistically. Nevertheless, this is not anticipated to have any impact of the outcome of the study. The issue is therefore not pursued.

Otherwise, none of the protocol amendments in the three studies are expected to have any impact on study integrity or outcome.

Efficacy data and additional analyses

Participant flow

In all three studies, the proportion of screened subjects not enrolled in the study was high (59-63%). For all studies, the main reason was that the subject did not qualify for enrolment based on the inclusion and exclusion criteria, including washout failure. The difficulties in predicting the numerical decrease in serum phosphate during a washout period is acknowledged.
Since the subjects were not yet randomised, this is not expected to impact study conduct or study outcome.

It is noted that depending on the reason for screen failure, subjects in Study 204 could have been re-assessed only once for trial entry at least 2 weeks after their original screen failure date. The Applicant was asked how many patients have been re-assessed and how many of them were finally included in the Study. This information was however not captured in the clinical database and was not further pursued.

Early termination due to treatment failure, i.e., having serum phosphorus ≥6.0 mg/dL or haemoglobin <9.0 g/dL for 2 consecutive study visits, was overrepresented in the placebo arm of Study 204 (11/74 for placebo versus 1/75 for Xoanacyl). Out of the 11 subjects with treatment failure in the placebo arm, 9 subjects failed the haemoglobin criterium. This may be indicative of a treatment effect in the Xoanacyl arm. Treatment failure was also numerically more common in the placebo arm (9 subjects [8%] versus 5 subjects [4%] in the Xoanacyl arm) in Study 306.
In the active-controlled period (i.e., up to Week 52) of Study 304, early withdrawal was more common in the Xoanacyl arm versus the active control (96/292 subjects [33%] for AVA 1014 versus 38/149 [26%] for the active control arm).
In Study 304, treatment failure was defined as serum phosphorus levels of >8.0 mg/dL, or as serum calcium levels of >10.5 mg/dL [2.52 mmol/L] if on calcium acetate. Upon request, the Applicant clarified that 14/289 (4.8%) subjects in the Xoanacyl treatment arm and 7/149 (4.7%) in the control arm were recorded as treatment failures. All subjects in the Xoanacyl arm and two subjects in the control arm reached the stipulated threshold of >8.0 mg/dL for 2 consecutive visits. The remaining five subjects in the control arm, all on calcium containing phosphate binders, reached the threshold for adjusted serum calcium >10.5mg/dL and were switched to Xoanacyl. All subjects were to continue in the study.

In neither study, there are any reports of "early treatment termination". This would mean that all subjects reported as early termination exited from both treatment and follow up. The Applicant clarified that subjects terminating the studies due to treatment failure also exited the study to receive a different treatment. For the remaining subjects (n=26 in study 204 and n=52 in Study 306), there seems to be no actions taken to keep participants ongoing in the studies after early treatment discontinuation. For both studies, data collection for discontinuations seems to be based on the date of drug discontinuation. The Applicant's reconstruction of subjects continuing the study after this date is not fully reliable. The majority of the subjects seems to have left the study when discontinuing treatment. This is not considered to affect the benefit/risk ratio for the product and the issue is therefore not pursued.

Baseline demographics

The upper limits of eligibility for Hgb in Study 204 and 306 (Hgb >9.0 and <12.0 g/dL and ≥9.0 and ≤11.5 g/dL, respectively) are close to the lower limit of normal (LLN) in women (12 g/dL). The resulting mean baseline Hgb was approximately 10.6 g/dL in Study 204 and approximately 10.4 g/dL in Study 306. For both studies, baseline mean TSAT and ferritin (approximately 21% and 112 ng/mL, respectively, for Study 204 and approximately 20% and 84 ng/mL, respectively, for Study 306) is indicative of a population with absolute and functional iron deficiency.
A discussion on the optimal ferritin levels for introducing and discontinuing iron supplementation in the CKD population is ongoing. Notwithstanding, the study population of both studies are supported by the recommendations in the 2012 KDIGO anaemia guideline, as discussed above.

Despite the differences in inclusion criteria for serum phosphate between Study 204 and study 306, baseline phosphate levels were similar: approximately 4.6 mg/dL in Study 204 and approximately 4.2 mg/dL in Study 306. Baseline serum phosphate in the two NDD studies are thus within the range of normal (Study 306) or very close to the upper limit of normal (ULN) (study 204) for serum phosphate in adults (4.5 mg/dL). It could be argued that there is a part of the study populations that may not be considered in need of phosphate lowering therapy outside dietary phosphorus restriction. In this context, the lack of washout period in Study 306 (see above) may have had impact on baseline serum phosphate.

The eligibility criteria in Study 304 are not considered adequate to create a study population suitable for assessment of the effect of Xoanacyl on iron deficiency anaemia.
The mean baseline Hgb was approximately 11.6 g/dL, ferritin approximately 600 mg/mL and TSAT approximately 31%. The minimum baseline serum ferritin of 11 ng/mL indicates that there was a fraction of the study population in clear need of additional iron substitution, whereas another fraction already at baseline lies over the ferritin level when discontinuation should be considered according to most recommendations, as indicated by a maximum baseline serum ferritin of >1600 ng/mL. Overall, the study population as a whole is not considered representative of a DD-population with iron deficiency since a substantial part of the population seems not in need of additional iron substitution. In the Xoanacyl SmPC, it is stated that the product should be used with caution if serum ferritin rises above 500 ng/mL and that discontinuation should be considered at 800 ng/mL. In the KDIGO 2012 guideline on anaemia, it is stated that iron administration is appropriate when bone marrow iron stores are depleted or in patients who are likely to have a clinically meaningful erythropoietic response. This does not seem to be the case for the Study 304 population.

The mean baseline Hgb is close to the lower limit of normal for Hgb and with eligibility criteria not requesting anaemia for inclusion, it is anticipated that there are study participants who per definition are not anaemic.
The efficacy in treating subjects with more severe anaemia cannot be assessed with available data

since no subgroup analysis for response in ferritin, TSAT, and Hgb based on baseline Hgb was planned or presented, presumably since the study was designed to study hyperphosphataemia.

Efficacy outcome: iron deficiency anaemia

All three studies met their (co-)primary endpoints. Study 306 and 304 met all their secondary endpoints. In study 204, the last secondary endpoint, eGFR, was not met. For all (co-)primary and secondary endpoints a sensitivity analysis was performed. The results of the sensitivity analyses were similar to the primary analyses with the exception of serum phosphate, which was a secondary endpoint in study 306.

NDD-population (Study 204 and Study 306)

The reported increase of TSAT and ferritin in the NDD-studies supports a restoration of iron stores with treatment.

In Study 204, the mean increase in Hgb was 0.4 g/dL, raising LS-mean Hgb from 10.5 at baseline to 10.9 g/dL Week 12. In Study 306, the mean increase in Hgb was 0.75 g/dL, raising LS-mean Hgb from 10.4 at baseline to 11.2 g/dL Week 16. There are additional components involved in the development of anaemia beside iron deficiency in the CKD population compared to a non-CKD population, for example erythropoietin deficiency, uremic toxins inhibiting erythropoiesis, and a shorter life span of red blood cells.
The Applicant provided a comparison between the magnitude of mean Hgb increase in Studies 204 and 306 and that in similar studies with other iron products, based on the SmPC of the other products. While it is acknowledged that the numerical improvements of Hgb in Studies 204 and 306 are in the same magnitude as described for the other products, comparisons between studies are notoriously difficult, since background settings, study populations, treatments, etc., are likely to differ between the studies. Notwithstanding, as pointed out by the Applicant, the probability of a reduced response to Xoanacyl in the NDD-population due to hepcidin is low since both transferrin and ferritin increased by treatment. Taking this into consideration, the reported increase in Hgb during treatment is considered adequate.

In summary, evidence for a positive effect of Xoanacyl on iron deficiency anaemia in the NDD-population based on the results from Study 204 and Study 306 have been presented. These are generally acknowledged, and an indication for treatment of iron deficiency (anaemia) in this population is considered approvable.

DD-population (Study 304)

The benefit of Xoanacyl on iron deficiency (anaemia) on the NDD-population could not be directly extrapolated to the DD-population, considering that the ability to take up peroral iron from the GI tract is decreasing with declining renal function and typically, peroral iron supplementation is insufficient in the DD-population.

At week 12, there was a small increase Hgb compared to baseline in the Xoanacyl arm. The magnitude of change from baseline is not clinically relevant and most probably within the margin of error for the analysis.
After this time point, Hgb decreased over time up to week 52 in both treatment arms. The difference between the treatment arms at week 52 reached a weak statistical significance in favour of the Xoanacyl treatment arm, but of no clinical relevance.

The Applicant stated that "the underlying iron deficiency and the challenge of treating it in the DD population is also demonstrated by the continued reduction in Hgb in the standard of care control arm over the 12-month active control period, despite permitting use of routine maintenance IV iron and ESA therapy". This is not fully agreed. Study 304 was an open label study. IV iron therapy was

permitted for subjects with serum ferritin ≤1000 ng/mL and TSAT ≤30% and ESA use was also permitted. The dosing/dose adjustments of IV iron and/or ESA were at the discretion of the Investigator or site. It is expected that investigators were aware of the recommendations from KDIGO on anaemia in CKD (KI_SuppCover_2.4.indd), and therefore would tend to decrease ESA to adjust Hgb to below 11.5 g/dL. It is also plausible that adjustments were made to keep ferritin levels within the recommended interval. Thus, it is conceivable that for both treatment arms, the development of Hgb does not entirely reflect the challenges in treating anaemia and iron deficiency in a DD population, but rather an active reduction of treatment to avoid overtreatment, as indicated by the decrease in IV iron and ESA in both arms.

Baseline ferritin and TSAT in Study 304 with ferritin around 600 ng/mL and TSAT around 31% are not indicative for iron deficiency. Still, an increase in ferritin from approximately 600 to approximately 900 ng/mL was reported. This may indicate that the increasing iron stores are not effectively used in haemoglobin synthesis, which could increase the risk for iron accumulation. This is accentuated by the observation that, as expected, neither sevelamer nor calcium acetate exerted any clinically relevant effects on TSAT and ferritin, and still, there were no clinically relevant differences in Hgb between the treatment arms at the end of the observation period. However, as pointed out by the Applicant, the fact that TSAT also increased speaks against functional iron deficiency and a major role of hepcidin. The Applicant highlights significantly lower use of IV iron in the Xoanacyl versus the control arm. The Applicant also points out a decrease in ESA use with Xoanacyl versus active control (756 units/d versus 993 units/d, respectively). The difference in ESA use between the treatment arms just barely reached statistical significance (p=0.0473). This may further question the relevance of the increased iron stores in this population.

In summary, the Study 304 study population is not considered adequate to evaluate whether Xoanacyl treatment would indeed normalise Hgb in an anaemic DD-population. Furthermore, the population in Study 304 is not representative for a population with iron deficiency. It could therefore be argued that the study population of Study 304 is also not adequate for assessment of treatment of iron deficiency. Nonetheless, there is indirect support for an effect of Xoanacyl on iron stores in the DD-population since both ferritin and TSAT levels increased during treatment with Xoanacyl despite reduced administration of IV iron and ESA. This indicates that the iron released from the product at least to some extent is in fact taken up from the GI-tract. In combination with a more stable Hgb curve despite a larger reduction in IV iron administration and a numerically larger reduction of ESA supplementation in the Xoanacyl treatment arm in Study 304, this is considered to be in support of some effect of Xoanacyl on iron levels in the DD-population. However, it is acknowledged that the effect size in the DD population is not known based on available data.

The Applicant has presented an article from the scientific literature (Block et al., 2019) as a key supportive study to bridge data from the NDD- to the DD-population. It is agreed with the Applicant that the findings in the study are of large interest, in particular data on a composite endpoint of death, dialysis and transplant. Data on Hgb, ferritin and TSAT could be considered supportive of a positive effect of Xoanacyl in the NDD-population. Nonetheless, as pointed out by the authors, data needs to be confirmed in placebo-controlled randomised clinical trials. The Applicant underlines that the study provides the bridge between studies that were conducted in pure NDD or DD populations. No data on the DD-population was however presented in the publication.

Efficacy outcome: phosphate

In procedure EMEA/H/C/003776/0000, FCCC was approved in the EU for both the NDD- and DD-population under the name Fexeric for the control of hyperphosphataemia in adult patients with chronic kidney disease (CKD). The approval was mainly based on data from Study 204 and Study 304. The

assessment in the Fexeric procedure is supported. No data changing the previous decision by the EC has been provided.

In Study 306, difference between the treatment arms reached statistical significance (p=0.02) at Week 16 using the pre-specified primary analysis (MMRM). Using a sensitivity analysis (an ANCOVA model based on LOCF methodology), the difference was no longer statistically significant (p=0.086). In absolute numbers, the decrease in serum phosphate in the study was small and the clinical relevance could be questioned. Notwithstanding, the primary objective for Study 306 was iron deficiency anaemia. The study is considered as a supportive study for hyperphosphataemia. Dose adjustments were primarily based on Hgb parameters and the phosphate eligibility criterium (serum phosphate ≥3.5 mg/dL [1.13 mmol/L]) seems primarily intended to mitigate the risk of hypophosphataemia. Study 306 is therefore considered a supportive study for hyperphosphataemia, and the weaker effect on serum phosphate is not pursued.

Wording of the indication

The initially proposed wording of the indication (*Treatment of iron deficiency anaemia (IDA) in adult CKD patients with elevated serum phosphorus*) was not fully agreed as elevated serum phosphorus should be described as an indication and not a description of the population to be treated. A restriction of the indication to the NDD-population was also requested.

The effect size on iron stores in the DD population is not known. However, it is considered that the results from Study 304 indicate that the use Xoanacyl as a phosphate binder in the DD-population should be limited to subjects with iron deficiency due to the risk of iron accumulation. To avoid different indications for the NDD- and DD-populations, the indication "*Treatment of concomitant elevated serum phosphorous and iron deficiency in adult patients with CKD"* is accepted, and section 4.2 and 4.4 of the SmPC updated accordingly. Specifically, monitoring of the effect as well as addition/reduction of other treatments for iron deficiency is crucial. Additionally, section 4.2 states that the effect of Xoanacyl on iron deficiency has not been assessed in DD-subjects without permitting concomitant treatment with intravenous iron and/or erythropoiesis-stimulating agent (ESA) as needed. The potential need for concomitant treatment with IV iron and/or ESA was reflected in section 4.4.

2.5.7. Conclusions on the clinical efficacy

Efficacy of Xoanacyl on hyperphosphataemia in subjects with CKD was shown for both the NDD- and the DD-populations in procedure EMEA/H/C/003776/0000. No new data has been provided. The claim "*Treatment of elevated serum phosphorous"* is therefore considered acceptable for both populations. The claim "*Treatment of iron deficiency"* is considered supported for the NDD-population. It is also considered that the results from Study 304 indicate that the use Xoanacyl as a phosphate binder in the DD-population should be limited to subjects with iron deficiency due to the risk of iron accumulation. To avoid different indications for the NDD- and DD-populations, the indication "*Treatment of concomitant elevated serum phosphorous and iron deficiency in adult patients with CKD"* is accepted.

2.5.8. Clinical safety

The safety evaluation is separated into the CKD population that is non-dialysis-dependent (NDD) and the CKD population that is dialysis-dependent (DD). The clinical safety assessment is based on 7 clinical studies (Table 24: S), 3 in the NDD CKD population and 4 in the DD CKD population together with one phase 4 study (COMPASS) and 3 extension studies.

Table 24: Summary of dosing and number of subjects treated in studies included in pooled safety analyses

Study	Starting dose (g/day)	Max dose (g/day)	Average daily dose, g/day (SD)	No. treated, AVA1014	No. treated, Control (type)
NDD Population					
Study 204	3	12	5.1 (1.51)	75	73 (placebo)
Study 306	3	12	5.0 (1.69) [d]	198 [a]	116 (placebo)
Study 207	1 [b]	2 [b]	1.2 (0.18)	32	NA
DD Population					
Study 304	6	12	8.78 (3.07) [e]	289	149 (phosphate binder) 95 (placebo)
Study 305	1, 6 or 8	1, 6, or 8	Fixed dose	151 (51, 52, 48 per group)	NA
Study 201	4.5 or 6	11.3	Not reported in CSR	55 (34 and 21 per group)	NA
Study PBB00101	2, 4 or 6	2, 4 or 6	Fixed dose	100 [c] (33, 34, 33 per group)	16 (placebo)

CSR = clinical study report; DBPC = Double-blind placebo-controlled; DD = dialysis-dependent; FCCC = Ferric Citrate Coordination Complex; NA = not applicable; NDD = non-dialysis-dependent; No. = number; SD = standard deviation

[a] Includes 117 subjects randomised to AVA1014 in DBPC Randomised Period and 81 who switched from placebo to AVA1014 in Extension Period

[b] Administered without food (at least 2 hours before/after meals or snacks), in all other studies study drug was administered with food

[c] Formulation was not AVA1014, but contained pharmaceutical grade FCCC

[d] Value for placebo-controlled Randomisation Period. In Extension Period mean dose (SD) was 3.9 (1.44) g/day for subjects continuing AVA1014 (it was reset to 3 g/day at start of Extension) and 4.7 (1.42) g/day in subjects switched from placebo to AVA1014

[e] Value for 52-week active control phase

2.5.8.1. Patient exposure

Across the 11 studies that have been used to describe the safety profile of Xoanacyl, a total of 1,260 unique subjects have been treated with at least one dose of Xoanacyl (or for 100 of these subjects, a product containing pharmaceutical grade FCCC), 643 of these are NDD subjects and 617 are DD subjects (see also tables below). Across these 11 studies, the starting dose ranged from 1 to 8 g/day and the maximum dose was 12 g/day. The majority of subjects who were DD had a dose ≥ 6 to < 9 g/day (51.2%), whereas the majority of subjects who were NDD had a dose > 3 to < 6 g/day (57.8%).

Table 25: Exposure profile from pooled NDD population (studies 204, 306 and 207)

Dose Parameter	All AVA1014 [a] (N=301)	Randomised Period	
		AVA1014 (N=190)	Placebo (N=188)
Duration of Exposure (Weeks) [b]			
Mean (SD)	13.01 (7.396)	12.75 (4.188)	12.08 (4.926)
Median	11.57	12.86	12.29
Min, Max	0.6, 26.0	1.0, 16.7	0.1, 18.1
Duration of Exposure by Category n (%)			
≤4 weeks	21 (7.0%)	14 (7.4%)	26 (13.8%)
> 4 to 8 weeks	81 (26.9%)	12 (6.3%)	12 (6.4%)
> 8 to 12 weeks	67 (22.3%)	31 (16.3%)	24 (12.8%)
> 12 to 16 weeks	45 (15.0%)	80 (42.1%)	86 (45.7%)
> 16 to 20 weeks	3 (1.0%)	53 (27.9%)	40 (21.3%)
> 20 weeks	84 (27.9%)	-	-
Cumulative Duration by Category n (%)			
Any exposure	301 (100%)	190 (100%)	188 (100%)
> 4 weeks	280 (93.0%)	176 (92.6%)	162 (86.2%)
> 8 weeks	199 (66.1%)	164 (86.3%)	150 (79.8%)
> 12 weeks	132 (43.9%)	133 (70.0%)	126 (67.0%)
> 16 weeks	87 (28.9%)	53 (27.9%)	40 (21.3%)
> 20 weeks	84 (27.9%)	-	-
Average Daily Dose (g/day) [c]			
Mean (SD)	4.71 (1.744)	5.37 (1.476)	5.73 (1.716)
Median	5.00	5.44	6.33
Min, Max	1.0, 8.3	2.3, 8.3	1.6, 8.6
Average Daily Dose by Category, n (%)			
<3 g/day	38 (12.6%)	3 (1.6%)	5 (2.7%)
≥3 to <6 g/day	174 (57.8%)	114 (60.0%)	82 (43.6%)
≥6 g/day	89 (29.6%)	73 (38.4%)	101 (53.7%)

N = Number of subjects in the treatment group (denominator for percentages); SD = Standard Deviation.
[a] Includes Study 306 and Study 204 double-blind AVA1014, Study 306 open-label Extension Period, and open-label Study 207. For any exposure, includes unique patients only.
[b] Treatment duration in weeks = (date of last dose - date of first dose + 1)/7.
[c] Average daily dose was calculated as the number of tablets taken divided by treatment duration in days.
Source: ISS for IDA Table 2.4.

Table 26: Exposure profile from pooled DD population (studies 304, 205, 201, and PBB00101)

Dose Parameter	All AVA1014 (N=557)	Active Control (N=149)
Duration of Exposure (Weeks)		
n	557	149
Mean (SD)	24.52 (24.089)	45.04 (15.383)
Median	4.86	52.14
Min, Max	-2.4, 60.9	-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%)
Average Daily Dose (g/day)		
n	557	147
Mean (SD)	6.14 (2.817)	5.78 (2.149)
Median	6.00	5.30
Min, Max	1.0, 12.0	1.3, 9.6
Average Daily Dose by Category, n (%)		
< 6 g/day	192 (34.5%)	-
≥ 6 to <9 g/day	285 (51.2%)	-
≥ 9 g/day	80 (14.4%)	-

N = Number of subjects in the treatment group (denominator for percentages); n = Number of subjects in the subset (numerator for percentages); SD = Standard Deviation.
Source: ISS for HyperP, Table 1.2.2, 2.1.1, Table 3.20.2

There was a similar duration of exposure across treatment groups in randomised periods with mean duration of exposure of 12.75 and 12.08 weeks in the Xoanacyl Randomised Period and Placebo Randomised Period groups, respectively, in the NDD pool. In the pooled DD population, there are differences in duration of exposure across the groups. The placebo study arm has 4-week duration only, after the 48-week positively controlled part and is not intended for collection of safety data. The differences in exposure time between randomised treatment groups in the DD-population hampers the possibility to draw conclusions on test vs placebo. The most relevant comparison is the 48 weeks period where Xoanacyl is compared with phosphate binders.

Subjects entering the study 304 could not be intolerant to the active control phosphate binders. Thus, safety data on patients who were intolerant to phosphate binders are available from the NDD pool only.

For details on demographics please see Table 12.

2.5.8.2. Adverse events

The total frequency of TEAE is high in both populations and all groups, which is expected considering the disease characteristics. Overall, in the NDD pool (Table 27), the recorded difference vs placebo is small, and this is the only reliable comparison vs placebo provided as the placebo group in the DD pool

is not intended to allow a balanced safety comparison. There are no apparent differences between Xoanacyl and the active control in study 304 in total amount of TEAEs (Table 28).

Table 27: Overview of TEAEs, pooled NDD safety population (studies 204, 306 and 207)

Category	All AVA1014 [a] (N=301)	Randomised Period	
		AVA1014 (N=190)	Placebo (N=188)
	n (%)	n (%)	n (%)
Any TEAE	216 (71.8%)	143 (75.3%)	116 (61.7%)
Any drug-related TEAE	95 (31.6%)	65 (34.2%)	39 (20.7%)
Any severe TEAE	25 (8.3%)	18 (9.5%)	17 (9.0%)
Any SAE	34 (11.3%)	20 (10.5%)	21 (11.2%)
Any drug-related SAE	0	0	0
Any death	3 (1.0%)	2 (1.1%)	2 (1.1%)
Any TEAE leading to treatment discontinuation	34 (11.3%)	22 (11.6%)	18 (9.6%)

N = Number of subjects in the treatment group (denominator for percentages); n = Number of subjects in the subset (numerator for percentages); NDD = Non-dialysis-dependent; SAE = Serious Adverse Event; TEAE = Treatment-emergent Adverse Event.
[a] Includes Study 306 and Study 204 double-blind AVA1014, Study 306 open-label Extension Period, and open-label Study 207.
Source: ISS for IDA Table 3.1

Table 28: Overview of TEAEs, pooled DD safety population (studies 304, 305, 201 and PBB00101)

Category	AVA1014		Active Control (N=149)	Placebo (N=111)
	All AVA1014 (N=557)	Study 304 (N=289) [a]		
	n (%)	n (%) [b]	n (%)	n (%)
Any TEAE	430 (77.2%)	261 (90.3%)	133 (89.3%)	44 (39.6%)
Any drug-related TEAE [c]	206 (37.0%)	105 (36.3%)	18 (12.1%)	4 (3.6%)
Any severe TEAE [d]	104 (18.7%)	71 (24.6%)	46 (30.9%)	7 (6.3%)
Any SAE [e]	142 (25.5%)	114 (39.4%)	73 (49.0%)	18 (16.2%)
Any drug-related SAE [c] [e]	6 (1.1%)	5 (1.7%)	4 (2.7%)	0
Any death	14 (2.5%)	13 (4.5%)	8 (5.4%)	0
Any TEAE leading to treatment discontinuation	67 (12.0%)	41 (14.2%)	14 (9.4%)	3 (2.7%)

DD = Dialysis-dependent; N = Number of subjects in the treatment group (denominator for percentages); n = Number of subjects in the subset (numerator for percentages); SAE = Serious Adverse Event; TEAE = Treatment-emergent Adverse Event.
[a] 52-week active-controlled Safety Assessment Period of Study 304.
[b] Denominators for percentages are based off of 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 AVA1014 group were counted as severe.
[e] SAEs and deaths up to 30 days after discontinuation/completion of study drug are counted.
Source: ISS for HyperP Table 3.1.1; Study 304 CSR, Table 14.3.1.1, Table 14.3.1.3, Table 14.3.1.4.

Common Adverse Events by System Organ Class

The evaluation by SOC provides an overview of the most common TEAEs. SOCs where there were at least 5% of subjects reporting TEAEs are presented (see tables below). The percentage of subjects

experiencing TEAEs in the "GI disorders" and "metabolism and nutrition disorders" SOCs were higher in the Xoanacyl groups compared to the placebo group (NDD pool). Compared to phosphate binders in the DD pool the only SOC where Xoanacyl had more TEAEs was "GI disorders".

Table 29: Adverse events by system organ class (SOCs with ≥ 5% of subjects in any treatment group), pooled NDD safety population

System Organ Class	All AVA1014 [a] (N=301)	Randomised Period	
		AVA1014 N=190)	Placebo (N=188)
	n (%)	n (%)	n (%)
Any TEAEs	216 (71.8%)	143 (75.3%)	116 (61.7%)
Cardiac Disorders	16 (5.3%)	10 (5.3%)	9 (4.8%)
Gastrointestinal Disorders	137 (45.5%)	94 (49.5%)	52 (27.7%)
General Disorders and Administration Site Conditions	25 (8.3%)	18 (9.5%)	24 (12.8%)
Infections and Infestations	53 (17.6%)	33 (17.4%)	35 (18.6%)
Injury, Poisoning and Procedural Complications	26 (8.6%)	19 (10.0%)	14 (7.4%)
Investigations	22 (7.3%)	14 (7.4%)	7 (3.7%)
Metabolism and Nutrition Disorders	51 (16.9%)	33 (17.4%)	20 (10.6%)
Musculoskeletal and Connective Tissue Disorders	15 (5.0%)	11 (5.8%)	13 (6.9%)
Nervous System Disorders	27 (9.0%)	21 (11.1%)	15 (8.0%)
Renal and Urinary Disorders	18 (6.0%)	12 (6.3%)	10 (5.3%)
Respiratory, Thoracic and Mediastinal Disorders	22 (7.3%)	13 (6.8%)	10 (5.3%)
Skin and Subcutaneous Tissue Disorders	12 (4.0%)	10 (5.3%)	8 (4.3%)
Vascular Disorders	21 (7.0%)	17 (8.9%)	15 (8.0%)

N = Number of subjects in the treatment group (denominator for percentages); n = Number of subjects in the subset (numerator for percentages); NDD = Non-dialysis-dependent; SOC = System Organ Class; TEAE = Treatment-emergent adverse event.
[a] Includes Study 306 and Study 204 double-blind AVA1014, Study 306 open-label Extension Period, and open-label Study 207.
Source: ISS for IDA Table 3.2.

Table 30: Adverse events by system organ class (SOCs with ≥ 5% of subjects in any treatment group), pooled DD safety population

System Organ Class	AVA1014		Active Control (N=149)	Placebo (N=111)
	All AVA1014 (N=557)	Study 304 (N=289) [a]		
	n (%)	n (%) [b]	n (%) [a] [b]	n (%)
Subjects with at least 1 TEAE	**430 (77.2%)**	**261 (90.3%)**	**133 (89.3%)**	**44 (39.6%)**
Blood and Lymphatic System Disorders	17 (3.1%)	16 (5.5%)	8 (5.4%)	0
Cardiac Disorders	51 (9.2%)	43 (14.9%)	26 (17.4%)	1 (0.9%)
Cardiac Disorders (Secondary)	10 (1.8%)	10 (3.5%)	11 (7.4%)	1 (0.9%)
Eye Disorders	15 (2.7%)	11 (3.8%)	9 (6.0%)	1 (0.9%)
Gastrointestinal Disorders	284 (51.0%)	163 (56.4%)	69 (46.3%)	14 (12.6%)
General Disorders and Administration Site Conditions	132 (23.7%)	98 (33.9%)	48 (32.2%)	6 (5.4%)
Infections and Infestations	131 (23.5%)	111 (38.4%)	62 (41.6%)	13 (11.7%)
Injury, Poisoning and Procedural Complications	106 (19.0%)	90 (31.1%)	56 (37.6%)	3 (2.7%)
Investigations	50 (9.0%)	40 (13.8%)	16 (10.7%)	2 (1.8%)
Metabolism and Nutrition Disorders	69 (12.4%)	50 (17.3%)	32 (21.5%)	4 (3.6%)
Musculoskeletal and Connective Tissue Disorders	78 (14.0%)	60 (20.8%)	38 (25.5%)	6 (5.4%)
Nervous System Disorders	77 (13.8%)	60 (20.8%)	32 (21.5%)	4 (3.6%)
Psychiatric Disorders	40 (7.2%)	30 (10.4%)	15 (10.1%)	1 (0.9%)
Respiratory, Thoracic and Mediastinal Disorders	85 (15.3%)	71 (24.6%)	45 (30.2%)	5 (4.5%)
Skin and Subcutaneous Tissue Disorders	53 (9.5%)	36 (12.5%)	27 (18.1%)	4 (3.6%)
Surgical and Medical Procedures	44 (7.9%)	40 (13.8%)	22 (14.8%)	1 (0.9%)
Vascular Disorders	72 (12.9%)	55 (19.0%)	37 (24.8%)	4 (3.6%)
Vascular Disorders (Secondary)	5 (0.9%)	3 (1.0%)	8 (5.4%)	0

DD = Dialysis-dependent; N = Number of subjects in the treatment group (denominator for percentages); n = Number of subjects in the subset (numerator for percentages); SOC = System Organ Class; TEAE = Treatment-emergent adverse event.
[a] 52-week active controlled period (Safety Assessment Period) of Study 304.
[b] Denominators for percentages are based off of subjects in the Safety Population.
Source: ISS for HyperP Table 3.2.1; Study 304 CSR, Ad Hoc Table 8.

Common Adverse Events by Preferred Term

In the NDD population, there were 6 TEAEs that occurred in ≥ 5% of subjects, all but 1 of which was in the GI Disorders SOC (PTs of faeces discoloured, diarrhoea, constipation, nausea and abdominal pain). The most common events while receiving Xoanacyl (> 10% in any Xoanacyl group) in the pooled NDD population were faeces discoloured, diarrhoea and constipation, all of which approximately twice as common in the test group than in the placebo group in randomised study periods (Table 31).

In the DD population, the majority of the most common TEAEs remained in the GI Disorders SOC and were the same PTs as listed under this SOC for the NDD population, with the addition of vomiting. Faeces discoloured and diarrhoea were more common in the AVA 1014 group than in the group receiving phosphate binders (Table 32).

Table 31: GI disorders by PT – NDD population

System Organ Class Preferred Term	All AVA1014 [a] (N=301)	Randomised Period	
		AVA1014 (N=190)	Placebo (N=188)
	n (%)	n (%)	n (%)
Gastrointestinal Disorders			
Faeces discoloured	59 (19.6%)	41 (21.6%)	0
Diarrhoea	57 (18.9%)	39 (20.5%)	23 (12.2%)
Constipation	43 (14.3%)	35 (18.4%)	19 (10.1%)
Nausea	22 (7.3%)	18 (9.5%)	8 (4.3%)
Abdominal pain	15 (5.0%)	9 (4.7%)	3 (1.6%)

Table 32: GI disorders by PT – DD population

System Organ Class Preferred Term	AVA1014		Active Control (N=149)	Placebo (N=111)
	All AVA1014 (N=557)	Study 304 (N=289) [a]		
	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders				
Diarrhoea	116 (20.8%)	74 (25.6%)	21 (14.1%)	7 (6.3%)
Faeces discoloured	108 (19.4%)	49 (17.0%)	0	1 (0.9%)
Nausea	62 (11.1%)	41 (14.2%)	21 (14.1%)	3 (2.7%)
Constipation	42 (7.5%)	23 (8.0%)	8 (5.4%)	0
Vomiting	38 (6.8%)	26 (9.0%)	22 (14.8%)	3 (2.7%)
Abdominal pain	27 (4.8%)	18 (6.2%)	9 (6.0%)	0

One common PT was pronounced hyperkalaemia (>6.5 mEq/L) which was higher in the test group than in placebo in the NDD pool (5.3 % vs 2.7 %) The group treated with phosphate binders in Study 304 had higher values than the Xoanacyl group making the interpretation difficult. The Applicant presented information about mean increase over time and explained that high values were transient. In addition, the number of cases with potassium values above the upper limit of normal was presented. The subgroups with diabetes and those with high ferritin/TSAT values was presented and discussed separately.

Adverse Events Considered Treatment-Related by Investigator

Similar events were assessed as treatment-related in the NDD and DD pool, with GI events being the most common. Overall, the percentage of subjects who experienced at least one related TEAE in the pooled NDD population was higher in the Xoanacyl group compared to the placebo group. In the placebo-controlled randomised period there was a higher percentage of subjects with at least 1 TEAE considered treatment-related in the Xoanacyl group (65/190, 34.2%) than in the placebo group (39/188, 20.7%). The most common treatment related TEAEs (> 10% of subjects in All Xoanacyl group) were faeces discoloured and diarrhoea.

Similar to the NDD population, the most common TEAEs for Xoanacyl in the DD population considered treatment-related by the investigator were in the GI Disorders SOC.

Adverse events by dose and duration

There was no prominent dose dependent increase in adverse events. The overall incidence of TEAEs was highest in the first 4 weeks of treatment. However, it was a possibility to apply dose adjustments

and pause treatment in case of iron overload making it difficult to assess the results from the pooled data as presented.

2.5.8.3. Serious adverse event/deaths/other significant events

Deaths

Overall, there were a total of 5 deaths in the pooled NDD population (2 from the placebo group and 3 from the group who received Xoanacyl) and 22 deaths in the pooled DD population. Of these 22, 14 subjects who were treated with Xoanacyl (14/557; 2.5%) and 8 subjects who were treated with active control phosphate binder (8/149; 5.4%). All deaths in the Pooled DD Safety Population occurred in Study 304. From the provided data, no obvious pattern or trends for specific adverse events resulting in death can be identified.

Other Serious Adverse Events

Among all subjects who received Xoanacyl in the NDD pool, 11.3% experienced an SAE, and in the placebo-controlled Randomised Period the percentages were 10.5% in the Xoanacyl group and 11.2% in the placebo group. The only individual SAEs that occurred in at least 1% of subjects treated with Xoanacyl were pneumonia, acute renal failure, and acute respiratory failure.

Overall, the percentage of subjects experiencing at least 1 SAE in the pooled DD population was lower in the Xoanacyl group (25.5%) compared to the active control group (49.0%). The pattern of events is similar to what was recorded overall and similar in the Xoanacyl group as in the patients receiving phosphate binders.

2.5.8.4. Adverse events in patients with elevated ferritin and TSAT levels

Ferritin and TSAT increased from baseline with Xoanacyl treatment. Increasing dose and increased duration of exposure to Xoanacyl tended to result in increased incidence of values higher than normal, most prominent in the DD population where 7.4 % of the patients had ferritin > 1500 ng/mL and 26% had recordings of TSAT > 50% at any time point post-baseline in the Xoanacyl group.

All of the subjects with maximum ferritin values ≥ 1500 ng/mL were in Study 304, and most had the maximum ferritin values > 1500 ng/mL after 12 or 24 weeks of treatment, whereas at least half of the subjects in the lower maximum ferritin groups were from studies of 4 weeks duration.

According to the applicant, examination by maximum ferritin category revealed no consistent pattern in the reported types of AEs by SOC.

2.5.8.5. Adverse events of special interest (AESIs)

The Applicant indicated certain adverse drug reactions associated with oral phosphate binders and/or with oral iron products and denoted these adverse events of special interest. These are gastrointestinal disorders, infections, cardiac disorders, hepatobiliary disorders and endocrine dysfunction. Besides gastrointestinal disorders there were no relevant findings following the applicant's assessment of data.

Gastrointestinal Disorders were the most frequent AEs for all subjects, and the incidence among subjects who received Xoanacyl (49.5%) was nearly twice that of placebo subjects (27.7%) in the Randomised Period (NDD population) (Table 31). In the DD population there was a slightly higher percentage of subjects in the Xoanacyl group that reported at least 1 GI Disorders AESI compared with active control (49.6% versus 45.6%). Faeces discoloured was the most frequent finding followed by diarrhoea, nausea and constipation (Table 32).

Gastrointestinal events often manifested within the first 4 weeks of treatment, although there were occasional reports of new-onset events with extended duration of treatment. Most GI events were generally well-tolerated; the percentage of subjects discontinuing due to GI events was 4.8% in the All Xoanacyl group (NDD population), and higher than the placebo group in the randomised period (5.3% in Xoanacyl group and 1.1% in placebo group). As per the NDD population, TEAEs that led to discontinuation in the DD population were most commonly in the GI Disorders SOC. The most common PT that led to discontinuation with Xoanacyl treatment was diarrhoea (3.6% of subjects).

2.5.8.6. Laboratory findings

There were deviations in phosphorous levels recorded with values below 2.0 mg/dL. Data collected on haematology, clinical chemistry and liver function tests (the latter for the NDD population only) revealed no significant findings. There was a certain number of subjects with increased values (3 x normal) in both populations, but the findings were few and transient. Xoanacyl treatment does not seem to be linked to hepatic toxicity.

For biomarkers for iron load, please see Adverse events in patients with elevated ferritin and TSAT levels above.

2.5.8.7. In vitro biomarker test for patient selection for safety

N/A

2.5.8.8. Safety in special populations

In the pooled safety populations, subgroup analyses for TEAEs by age, gender, race, CKD stage (NDD population), diabetes status and weight were performed. In addition to these, subgroup analyses based on liver dysfunction were performed for the DD population.

There were no specific findings related to gender, race, or weight in either of the population and none of CKD stage in the NDD population.

The pattern of adverse events is increasing with age as expected.

Table 33: Pooled NDD population: summary of TEAEs by age category

	Active All Xoanacyl (N=301)				Active Double-blind Xoanacyl (N=190)				Comparator Placebo (N=188)			
MedDRA Terms	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)	Age <65 n (%)	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
N	115	112	66	8	78	68	41	3	81	68	29	10
Total AEs	88 (76.5)	73 (65.2)	49 (74.2)	7 (87.5)	62 (79.5)	48 (70.6)	31 (75.6)	3 (100.0)	54 (66.7)	42 (61.8)	16 (55.2)	4 (40.0)
Serious AEs – Total	11 (9.6)	12 (10.7)	7 (0.6)	4 (50.0)	7 (9.0)	8 (11.8)	3 (7.3)	2 (66.7)	13 (16.0)	5 (7.4)	3 (10.3)	0
Fatal	1 (0.9)	2 (1.8)	0	0	0	2 (2.9)	0	0	1 (1.2)	1 (1.5)	0	0
Hospitalisation/ prolong existing hospitalisation	SAE category not reported in clinical database											
Life-threatening	SAE category not reported in clinical database											
Disability/ incapacity	SAE category not reported in clinical database											
Other (medically significant)	SAE category not reported in clinical database											
AE leading to drop-out [a]	11 (9.6)	11 (9.8)	8 (12.1)	4 (50.0)	7 (9.0)	8 (11.8)	5 (12.2)	2 (66.7)	11 (13.6)	5 (7.4)	2 (6.9)	0
Psychiatric disorders	3 (2.6)	2 (1.8)	1 (1.5)	0	0	2 (2.9)	0	0	2 (2.5)	1 (1.5)	1 (3.4)	0
Nervous system disorders	9 (7.8)	11 (9.8)	6 (9.1)	1 (12.5)	9 (11.5)	7 (10.3)	4 (9.8)	1 (33.3)	8 (9.9)	4 (5.9)	2 (6.9)	1 (10.0)
Accidents and injuries	11 (9.6)	9 (8.0)	1 (1.5)	2 (25.0)	9 (11.5)	6 (8.8)	1 (2.4)	0	8 (9.9)	0	4 (13.8)	1 (10.0)
Cardiac disorders	4 (3.5)	8 (7.1)	3 (4.5)	1 (12.5)	1 (1.3)	6 (8.8)	2 (4.9)	1 (33.3)	3 (3.7)	3 (4.4)	3 (10.3)	0
Vascular disorders	6 (5.2)	7 (6.3)	8 (12.1)	0	4 (5.1)	6 (8.8)	7 (17.1)	0	5 (6.2)	4 (5.9)	4 (13.8)	2 (20.0)
Cerebrovascular disorders	0	2 (1.8)	0	0	0	0	0	0	0	0	0	0
Infections and infestations	23 (20.0)	21 (18.8)	8 (12.1)	1 (12.5)	17 (21.8)	12 (17.6)	4 (9.8)	0	15 (18.5)	13 (19.1)	7 (24.1)	0
Anticholinergic syndrome	4 (3.5)	9 (8.0)	2 (3.0)	0	3 (3.8)	7 (10.3)	0	0	5 (6.2)	3 (4.4)	0	1 (10.0)

Diabetes is the highest risk factor for development of CKD and there were more subjects with a history of diabetes than no such history. Subjects with diabetes tended to have a higher overall incidence of at least 1 TEAE than those without diabetes (77.3% versus 70.7% in the Xoanacyl group in the NDD pool and 80.3% versus 73.1% respectively in the DD pool). With respect to specific TEAEs, the diabetes subgroup demonstrated a higher incidence of pronounced hyperkalaemia and hyperglycaemia in the NDD population, but there were no notable differences in incidence with respect to GI disorders.

Of specific relevance for the diabetic subpopulation is serum glucose concentrations. The incidence of high glucose (above 13.9 mmol/L) demonstrated a relationship with increasing Xoanacyl dose, with the higher doses resulting in higher incidence (24.6 %) than the lower dose (18.4) % in the NDD population. In the NDD pool (randomised periods), there were 6 patients (4.5 %) experiencing an

event of high glucose (above 13.9 mmol/L) in the Xoanacyl group compared to 1 patient (0.8 %) in the placebo group.

All patients with hepatic impairment at baseline (11% in NDD and 12% in DD population) were treated with a starting dose of 3 or 6 tablets per day. The percentage of subjects who experienced at least 1 TEAE was similar to subjects without liver dysfunction (77.6% versus 77.1%), TEAEs leading to study drug discontinuation (11.9% versus 12.0%), GI Disorders (51.0 versus 50.7) and deaths (4.5% versus 2.2%).

2.5.8.9. Discontinuation due to adverse events

In the Pooled NDD Safety Population, 11.3% of subjects who received Xoanacyl discontinued study treatment. During the Randomised Period, 11.6% and 9.6% of subjects in the Xoanacyl and placebo groups discontinued due to one or more TEAE, respectively. In the Pooled DD Safety population, 12.0% of subjects in the All Xoanacyl group discontinued due to one or more TEAEs. In the active control group, which included only subjects who were not intolerant to their phosphate binder, the percentage of subjects was 9.4%. TEAEs that led to discontinuation were most common in the GI Disorders SOC, with diarrhoea as the most prevalent PT recorded. The cut off for presentation in the clinical summary is 2 subjects sharing the same reason for discontinuation in the NDD pool whereas in the DD pool, reason for discontinuation are listed at a higher level i.e., 2 % of subjects.

2.5.8.10. Post marketing experience

The medicinal product has been approved in EU under the name Fexeric but was never marketed and therefore there is no post marketing experience in the EU. Data on cumulative exposure is provided from the most recent Periodic Benefit Risk Evaluation Report (PBRER) with data lock point of 23 Sep-2023 in the US (30,000 to 61,000 patient years [PY]), Japan (85,000 PY), Taiwan (875 PY) and Korea (7 PY). On request, the applicant discussed available global post-marketing safety data and presented safety signals investigated. The pattern of adverse events reported in the post-marketing setting was fully in line with study data as presented in this report. A number of safety signals have been validated but there is none raising concerns. They were all refuted.

The US product information referred to lists discoloured feces, diarrhoea, constipation, nausea, vomiting, cough, abdominal pain, and hyperkalaemia as most common adverse reactions (incidence ≥5%). Data on severity are not given.

2.5.9. Discussion on clinical safety

Exposure

The database consists of a number of studies where Studies 204 and 306 in the NDD population and Study 304 in the DD-population were controlled trials pivotal for assessment of efficacy. Across all the 11 studies used to describe the safety profile of Xoanacyl, a total of 1,260 unique subjects have been treated with at least one dose of Xoanacyl (or for 100 of these subjects, a product containing pharmaceutical grade FCCC), 643 of these are NDD subjects and 617 are DD subjects. Across these 11 studies, the starting dose ranged from 1 to 8 g/day and the maximum dose was 12 g/day.

Safety data are summarised into pooled populations for NDD and DD respectively. For NDD, placebo-controlled data are available for 12 weeks (Study 204) and 16 weeks (Study 306). In the DD-population there is no valid placebo-control as the only placebo-controlled data (besides dose-finding) is from a 4-week period where patients had already been treated for 52 weeks with Xoanacyl (Study

304). Therefore, for the evaluation of safety in the Pooled DD Population, the comparison is primarily to the active control phosphate binder arm from Study 304.

In pivotal trials 273 NDD and 289 DD patients were included and in addition there are data from supportive studies. The size of the safety database is deemed sufficient. Since approval of Fexeric, the Study 306 has been added and more data on long term safety are available (Study 307 which is a 48-week extension to Study 304 and the phase 4 study 402 which was listed in the RMP for Fexeric).

The amount of placebo-controlled data is nevertheless limited in the DD population as the placebo-controlled phase in Study 304 takes place in the end of a 52-week period where the comparator was a phosphate binder. It is difficult to draw conclusions from this comparison. It is also noted that subjects entering the study 304 could not be intolerant to the active control phosphate binders. Thus, safety data on patients who are potentially intolerant to phosphate binders are available from the NDD pool only.

Adverse events

There was an overall higher percentage of subjects experiencing at least one TEAE in the Xoanacyl groups compared to the placebo groups (for the DD-population the applicant has included a comparison to the placebo group although this is not a fully valid comparison). Overall, 75% in the treatment group and 62% in the placebo group experienced adverse events in the NDD patient pool. The corresponding numbers for the DD pool are 90% vs 40% for the Xoanacyl population and placebo.

The pattern of most common TEAEs recorded are in line with the mode of action of the compound. Oral iron supplement is known to give raise to GI disturbances, and this is the far most common adverse events where there is a difference vs placebo.

The pooled analysis in the DD population demonstrated that there were more SOCs with TEAEs (>10% of subjects) compared to the NDD population. According to the Applicant, this is expected considering both the clinical status of the subjects and the longer duration of follow-up. This is agreed.

A thorough assessment of related TEAEs in the DD population is difficult as, as outlined above, the active control group only included subjects who were not intolerant to their phosphate binder and test and placebo groups are not comparable. However, the observed TEAEs deemed related to treatment are in line with what could be expected considering the mode of action of the compound.

Among subjects treated with Xoanacyl at any time in the NDD population, 8.3% experienced a severe event. The percentage of subjects with severe TEAEs was similar between Xoanacyl group and placebo group (9.5% and 9.0%, respectively). In the DD population, 18.7% experienced a severe event.

Dose and time dependency

There seems to be some dose dependency in the incidence of TEAEs, most apparent for the DD population where there was a difference also for severe TEAEs between dose groups. Firm conclusions should not be drawn as data are limited but some dose dependency is expected considering the particulars of the compound. Dose dependency for GI disturbances for oral iron supplement is well known.

The applicant presents data on TEAE adjusted for treatment duration and suggests that drug tolerance should be independent on study duration with GI events being more of a problem the first weeks after start of treatment. There was however a possibility to apply dose adjustments and pause treatment in case of iron overload making it difficult to assess the results from the pooled data as presented. The more apparent difference in total number of AEs recorded in the DD population could nevertheless be

due to the placebo-controlled part of the study being performed at the end of a 52-week treatment period.

Adverse events of special interest

The applicant indicated certain adverse drug reactions associated with oral phosphate binders and/or with oral iron products and denoted these adverse events of special interest. This is appropriate.

Of the adverse events of special interest presented only GI-tract disturbances are of concern. Else there were no significant findings in the list of AESIs. Thus, none of the others (infections, cardiac disorders, hepatobiliary disorders and potential endocrine dysfunction) warrants further investigation.

Gastrointestinal disorders were the most frequent AEs for all subjects, and the incidence among subjects who received Xoanacyl (49.5%) was nearly twice that of placebo subjects (27.7%) in the randomised period (NDD population). In the DD population there was a similar percentage of subjects in the Xoanacyl group that reported at least 1 GI Disorders AE compared with active control (49.6% versus 45.6%). Faeces discoloured was the most frequent finding followed by diarrhoea, nausea and constipation. Gastrointestinal events often manifested within the first 4 weeks of treatment, although there were occasional reports of new-onset events with extended duration of treatment. Most GI events were generally well-tolerated but there were serious events recorded and a number of patients discontinued due to GI events (5.3% in Xoanacyl group and 1.1% in placebo group in the NDD population). Upon request, the SmPC Section 4.4 was updated with criteria for monitoring and recommendations for treatment discontinuation and a summary description was presented section 4.8.

Upon request, possible adverse events linked to citrate exposure was presented by the applicant. The applicant explained that the characteristics of the FCC complex are such that rapid uptake of citrate is unexpected under the conditions prevailing in the GI-tract. There is no complete separation of all citrates from the complex but amorphous precipitate is built up where ferric iron, citrate and phosphate are covalently bound and finally excreted in the stool. There is nevertheless some uptake of citrate which according to the applicant could be positive as it might provide an alkalising effect helping to balance chronic metabolic acidosis in patients with CKD. There is a certain increase in serum bicarbonate values over time in the NDD population (in average an increase with 1.57 mEq/L over the treatment period) as compared to placebo (0.2 mEq/L increase). The increase was more evident in patients with diabetes. In the DD-population, there was an increase in both study arms of the same magnitude in the test group in NDD population.

There was a certain number of subjects in both populations with increased liver enzymes values (3 x normal), but the findings were few and transient. Xoanacyl treatment does not seem to be linked to hepatic toxicity.

Serious adverse events and deaths

Among subjects treated with Xoanacyl at any time, 8.3% had a severe event in the NND population and 18.7% in the DD population. In the randomised periods (NDD population), the percentage of subjects with severe TEAEs was similar between Xoanacyl group and placebo group (9.5% and 9.0%, respectively).

In the Pooled NDD Safety Population, there were no deaths that were considered related to study treatment. Overall, there were a total of 5 deaths, 3 subjects who were treated with Xoanacyl (3/301; 1.0%) and 2 subjects treated with placebo (2/188; 1.1%). There was a total of 22 deaths in the pooled DD population; 14 subjects who were treated with Xoanacyl (14/557; 2.5%) and 8 subjects who were treated with active control phosphate binder (8/149; 5.4%). All deaths in the Pooled DD Safety Population occurred in Study 304.

Discontinuations

In the Pooled NDD Safety Population, 11.3% of subjects who received Xoanacyl discontinued study treatment. During the Randomised Period, 11.6% and 9.6% of subjects in the Xoanacyl and placebo groups discontinued due to one or more TEAE, respectively. In the Pooled DD Safety population, 12.0% of subjects in the All Xoanacyl group discontinued due to one or more TEAEs. In the active control group, which included only subjects who were not intolerant to their phosphate binder, the percentage of subjects was 9.4%. The dominating SOCs TEAE leading to discontinuation, in the NDD and DD population, were GI Disorders and the most common individual TEAE leading to discontinuation was diarrhoea (see AESI above). It is nevertheless unclear why different cut offs for presentation (2 subjects and 2 % of subjects respectively) were applied for the NDD and DD population.

Special populations

Subgroup analyses for TEAEs by age, gender, race, CKD stage, diabetes status and weight were performed. The only special population where there was an imbalance between test group vs placebo was the diabetes population. There is limited data available from elderly people (>75 years of age), this is mentioned in the SmPC.

Subjects with diabetes tended to have a higher overall incidence of at least 1 TEAE than those without diabetes (77.3% versus 70.7% in the Xoanacyl group) in the NDD pool. Within the Xoanacyl group (NDD population), there was no single SOC that had a meaningfully higher incidence for the Diabetes subgroup as compared to the No Diabetes subgroup. For the total population, the incidence of PCS high glucose (> 13.9 mmol/L) appears to demonstrate a dose dependent relationship with increasing Xoanacyl dose. Also, subgroup analyses showed that the diabetes subgroup in NDD Study population demonstrated a higher incidence of hyperglycaemia (above 13.9 mmol/L) with 6 patients (4.5 %) experiencing an event of high glucose in the Xoanacyl group compared to 1 (0.8 %) patient in the placebo group.

Adverse events in patients with elevated ferritin and TSAT levels are presented separately. Ferritin increased with time with quite a few subjects having high maximal values in the study. The subjects included in the DD population were nevertheless not necessarily iron deficient at inclusion and intravenous iron supplementation was applied in parallel to ASA1014 in Study 304. Thus, the data presented from this study is not fully relevant for the population intended for treatment. According to the applicant, only one patient experienced iron overload. This subject was later diagnosed with (primary) haemochromatosis. There are nevertheless a number of other cases (mainly in the DD population) with iron overload based on very high (>1500 ng/mL) ferritin levels and TSAT > 70 %. This is of concern as iron overload is associated with decreased bone mineral density. In a recent article (Burden *et al.,* 2024) data showed that subjects with ferritin > 1000 ng/mL had a 91% increased risk of any fracture (HR 1.91 [1.73-2.16]) and a 2.5-fold increased risk of vertebral fractures (HR 2.51 [2.01-3.12]). To avoid such high levels in clinical practice, the applicant suggested SmPC-wordings recommending monitoring with dose reduction or temporary discontinuation to be considered if serum ferritin is persistently above 800 ng/mL for DD patients and 600 ng/mL for NDD patients. Nevertheless, the applicant refers to a paper (Macdougall et al 2019) where it is concluded that ferritin (up to 700 ng/mL) and TSAT (up to 40%) levels are beneficial without safety concerns in DD patients receiving intravenous iron supplementation. This is acknowledged and deemed to be appropriate thresholds for dose adjustments.

Examination by maximum ferritin category revealed no consistent pattern in the reported types of AEs by SOC. Adverse events were apparently more common in the highest ferritin/TSAT groups but as pointed out by the applicant, these data should be interpreted with caution as the difference was consistent throughout the treatment groups (including placebo in the NDD population). These high

values should nevertheless be avoided as ferritin levels above 700 ng/mL and TSAT above 40% are not anticipated to give additional effect and would increase the risk for iron overload.

Some cases with high TSATs showed lability (abrupt, non-sustained changes) but not for ferritin. The applicant argued that this is suggestive of phenomena other than those expected as a result of iron repletion with continued dosing and suggest that this could be due to the timing of the dose administration relative to the blood draws was not standardised. This is acknowledged. For this reason, ferritin might be a more reliable parameter when assessing risk for AEs linked to iron overload. Data on AEs by subgroups (≤ 50% versus >50 % and ≤ 70% versus >70 %) based of TSAT did nevertheless not raise any concerns. There are some indications of higher frequency of AEs in subjects with high TSAT but the data are difficult to interpret as the possible increase was recorded in all treatment groups including placebo.

Managing serum phosphorus was together with managing iron deficiency the primary objectives of studies conducted. Titration schemes were applied to manage phosphorous levels, but still there were subjects recorded with levels below 2.0 mg/dL. According to the SmPC section 4.2 and 4.4, serum phosphorus concentrations should be monitored within 2 to 4 weeks of starting or changing the dose of Xoanacyl, and approximately every 2-3 months when stable.

Product information

The SmPC text suggested by the applicant is partly similar and partly different to the previously approved SmPC for Fexeric. The texts in Section 4.4 and 4.8 was updated on request. As the pattern of adverse events are overall similar between the two populations, there is one table covering both populations.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

The population investigated differs from the population intended for treatment as many subjects in the DD-population had iron stores (largely) exceeding the ferritin levels indicative of an absolute or functional iron deficiency, and therefore would probably not have been considered for iron treatment in a clinical setting. There were also such patients included in the NDD-studies, but to a much lesser extent. The safety pattern recorded is nevertheless as expected from oral iron supplementation, predominately GI-tract disturbances.

2.6. Risk Management Plan

2.6.1. Safety concerns

None

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

None.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. 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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The originally proposed indication for Xoanacyl in the EU was: *Treatment of iron deficiency anaemia (IDA) in adult CKD patients with elevated serum phosphorus.*

Chronic kidney disease (CKD) is a structural or functional abnormality of the kidneys that has health implications and been present for more than 3 months. Besides the obvious effects on excretion of waste products and superfluous fluids with impaired renal function, there is a multitude of secondary problems arising with progressing CKD, such as hyperphosphataemia, secondary hyperparathyroidism, hyperkalaemia, iron deficiency, anaemia, hypertension, and metabolic acidosis.

The aim of the therapy is to address iron deficiency (anaemia) in subjects with hyperphosphataemia, thereby impacting two secondary problems.

3.1.2. Available therapies and unmet medical need

The clinical management of CKD patients with iron deficiency and elevated phosphorus is individualised based on the clinical status of the patient and level of kidney impairment and currently requires each aspect to be managed by different therapies. There is no other product on the EU-market intended for use in subjects with both iron deficiency and hyperphosphataemia.

Iron deficiency anaemia

Iron supplementation is widely used in CKD patients to treat iron deficiency, prevent its development in erythropoiesis stimulating agent (ESA) treated patients, raise Hb levels in the presence or absence of ESA treatment, and reduce ESA doses in patients receiving ESA treatment.

There are several oral and intravenous (IV) iron products available for treatment of iron deficiency (anaemia) in the EU, both groups with advantages and disadvantages. Among the adverse reactions with oral iron products is a well-known high rate of GI side effects contributing to poor adherence to therapy. Furthermore, the efficacy of oral iron supply in the DD-population is often low. Disadvantages with IV iron includes hypersensitivity reactions and potentially putting venous capital for arteriovenous fistulae creation at jeopardy.

Hyperphosphataemia

A variety of phosphate-binding agents have been used clinically. These include aluminium salts, calcium salts, sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate.
Velphoro is another iron-based phosphate binder centrally approved in the EU. The active substance in Velphoro is sucroferric oxyhydroxide. Velphoro is indicated for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD) and in paediatric patients 2 years of age and older with CKD stages 4-5 (defined by a glomerular filtration rate).

While other products to treat each of the conditions above are available, there is no other product on the EU-market intended for use in subjects with both iron deficiency and hyperphosphataemia. Ferric citrate coordination complex has a dual mechanism of action, one that is associated with providing a source of ferric iron and one associated with decreasing the absorption of phosphorous. The dual

mechanism of action result in a direct impact on reducing functionally active intact fibroblast growth factor 23 (iFGF-23).

3.1.3. Main clinical studies

Three studies were determined to be pivotal for efficacy:

Study 204 was a Phase 2, multicentre, randomised, double-blind, placebo-controlled (DBPC), study in adult subjects with NDD CKD (eGFR < 60 mL/min per 1.73m2) and iron deficiency anaemia (IDA) (Hgb >9.0 g/dL and <12.0 g/dL, TSAT≤ 30%, ferritin ≤ 300 ng/mL at screening) together with elevated serum phosphorous (≥ 4.0 mg/dL and < 6.0 mg/dL [1.29-1.94 mmol/l] at screening or after washout if applicable). A total of 149 subjects were randomised (75 to Xoanacyl and 74 to placebo) and began treatment with Xoanacyl at 3 g/day (3 tablets) or placebo. Subjects were followed up for 12 weeks post-randomisation (Treatment Period).

Study 306 was a Phase 3, multicentre, randomised study with two Study Periods: the Randomised Period (16-week DBPC) and the Extension Period (8-week, single-arm, open-label). Adult subjects with NDD CKD (eGFR < 60 mL/min per 1.73m^2) and IDA (Hgb >9.0 g/dL and <11.5 g/dL, TSAT≤ 25%, ferritin ≤ 200 ng/mL at screening) were included. Subjects were intolerant or had an inadequate therapeutic response to oral iron supplements (in the opinion of the Investigator) and had to have serum phosphorous ≥ 3.5 mg/dL. A total of 234 subjects were randomised (117 in Xoanacyl group and 117 in placebo group) and began treatment with 3 g/day of Xoanacyl (3 tablets) or placebo. Subjects who completed the 16-week randomised period could enter an extension period, during which all subjects were treated with Xoanacyl, starting with a dose of 3 tablets per day, regardless of the previous Xoanacyl dose for subjects who had received Xoanacyl in the randomised period.

Study 304 was a phase 3, multicentre, randomised, open-label study with two controlled periods: an active-controlled period (52-weeks) followed by a placebo-controlled period (4 weeks). Adult subjects with DD CKD with elevated serum phosphorous (≥ 6 mg/dL [1.94 mmol/L] after washout) were included. Eligibility criteria for iron parameters were TSAT <50% and ferritin <1000 ng/mL. No criteria for Hgb were given. During the 52-week active-controlled period, 441 subjects were randomised in a 2:1 ratio to Xoanacyl (n=292) or to active control (calcium acetate, sevelamer carbonate, or a combination of both at the discretion of the investigator) (n=149). The initial dose for subjects receiving Xoanacyl was 6 g/day (6 tablets) or calcium acetate and/or sevelamer carbonate. At the end of the 52-week period, subjects in the Xoanacyl arm were re-randomised into the placebo-controlled period in a 1:1 ratio to continue their Xoanacyl or take placebo tablets and were followed for a further 4 weeks (to Study Week 56). This was to evaluate the non-EU primary endpoint, in which the effect on hyperphosphataemia versus placebo was assessed

Iron deficiency endpoints

Iron stores were evaluated by change from baseline in serum ferritin and TSAT. TSAT was a (co)-primary endpoint in study 204 and a secondary endpoint in Study 306 and 304. Ferritin was a secondary endpoint in all three studies.

Anaemia was evaluated by change from baseline in Hgb, which was a secondary endpoint in Study 204 and Study 306.

Hgb responder rate defined as the proportion of subjects achieving an increase in Hgb of ≥1.0 g/dL at any point between baseline and the end of the randomised period (Week 16), was the primary endpoint in study 306.

There was no haemoglobin-related endpoint in Study 304; however, change from baseline in Hgb was provided as a post-hoc analysis.

Hyperphosphataemia endpoints

Change from baseline in serum phosphate was a co-primary endpoint in Study 204 and a secondary endpoint (last in hierarchy) in Study 306. In Study 304, non-EU primary endpoint was change in serum phosphate versus placebo during the last four weeks of the study. The EU primary endpoint was non-inferiority analysis of change from baseline versus active control.

3.2. Favourable effects

Iron deficiency

Effect of Xoanacyl on TSAT (increase from baseline):

- In NDD Study 204, TSAT increased with LS mean 10.2 percentage points from baseline 21.6 % in the Xoanacyl arm compared to -1.1 percentage points from 21 % in the placebo arm (difference between treatment arms LS mean [SE] 11.3 [1.7] percentage points; p<0.001).

Effect of Xoanacyl on Hgb (increase from baseline) in the NDD studies:

- In study 306, 52% of all subjects reached an increase in Hgb of ≥1.0 g/dL at any point between baseline and the end of the Randomised Period (Week 16) compared to 19% in the placebo arm (difference between treatment arms [95% CI] 33.0 [21.4, 44.6] %; p<0.001).

Supportive evidence arises from the secondary endpoints (TSAT% increase, Hgb increase and ferritin increase) shown in the effects table below.

Hyperphosphataemia

Effect of Xoanacyl on serum phosphate (decrease from baseline) in the NDD studies.

- In NDD Study 204, phosphate decreased with LS mean -0.7 mg/dL from baseline 4.5 mg/dL in the Xoanacyl arm compared to -0.2 mg/dL from 4.7 mg/dL in the placebo arm (difference between treatment arms LS mean [SE] -0.5 [0.11] g/dL; p<0.001).

Effect of Xoanacyl on serum phosphate (decrease from baseline) in the DD study 306.

- Phosphate decreased with mean -2.0 mg/dL at Week 12 from 7.41 mg/dL at baseline in the Xoanacyl arm compared to a decrease of 2.2 mg/dL from 7.46 mg/dL in the sevelamer arm and of 2.2 mg/dL from 7.56 mg/dL in the "all active controls" arm (treatment ratio 1.029 with a 95% CI of 0.959 to 1.104 versus sevelamer and 1.016 with a 95% CI of 0.960 to 1.075 versus all active controls). Non-inferiority was prespecified as the upper bound of the 2-sided 95% confidence interval for the treatment ratio laying below 1.2.

3.3. Uncertainties and limitations about favourable effects

The eligibility criteria in Study 304 reflects that this study was primarily designed to assess the Xoanacyl effect on hyperphosphataemia. There were no eligibility criteria or primary/secondary endpoints related to haemoglobin. The eligibility criteria for TSAT and ferritin are more suitable for minimising the risk of iron overload during treatment than creating a study population suitable for evaluating the effect of Xoanacyl on iron deficiency anaemia. This is reflected in the resulting study population. Based on this, the support for "treatment of iron deficiency" in the DD-population is weak.

The effect size on iron stores in the DD population is not known, nor assessable, from the data provided.

There are some additional unclarities, including the participant flow in Studies 204 and 306, the number and proportion of subjects on IV iron and on ESA at baseline in Study 304 and whether the less frequent monitoring of iron parameters introduced in protocol amendment 2 in study 304 affected the study results.

3.4. Unfavourable effects

Safety data are presented as two pooled populations, i.e., patients with and without need for dialysis. The total frequency of TEAE is high in both populations and all groups. In the NDD-pool (randomised period) 75.3 % experienced an adverse event compared to 61.7 % in the placebo group. Comparative data from DD-patients are available from Study 304 were 90.3 % experienced adverse events, i.e., similar frequency as the active control with phosphate binders (89.3 %).

The percentage of subjects experiencing TEAEs in the "GI disorders" and "metabolism and nutrition disorders" SOCs were higher in the Xoanacyl groups compared to the placebo group (NDD pool) with 49.5 % vs 27.7 % and 17.4 % vs 10.6 %, respectively. Else there were minor differences vs placebo at SOC level.

The most common GI-tract event recorded was faeces discoloured and diarrhoea (both ~20 %) followed by nausea and constipation (at ~10 %). A higher incidence of diarrhoea in the Xoanacyl arm compared to active control (25.6% vs 14.8%) in Study 304 is noted.

In the NDD pool a common finding in the SOC "metabolism and nutrition disorders" was pronounced hyperkalaemia (i.e. >6.5 mEq/L), (5.3 % vs 2.7 % in test and placebo group respectively). In addition, there was an increase from baseline in mean serum carbon dioxide/bicarbonate levels recorded in the pivotal NDD-studies. Mean change from baseline at the end of the randomised period was +1.2 mEq/L in the test group versus +0.1 mEq/L in the placebo group in Study 204.

Of specific relevance for the diabetic subpopulation is serum glucose concentrations. The incidence of high glucose (above 13.9 mmol/L) demonstrated a relationship with increasing Xoanacyl dose, with the higher doses resulting in higher incidence (24.6 %) than the lower dose (18.4 %) in the NDD population.

There were excursions in phosphorous levels recorded with values below 2.0 mg/Dl and also signs of iron overload, especially in the DD population where in the DD population where 7.4 % of the patients had ferritin > 1500 ng/mL and 26% had recordings of TSAT > 50% at any time point post-baseline in the Xoanacyl group.

3.5. Uncertainties and limitations about unfavourable effects

There are uncertainties with regard to severity of adverse events, especially GI-tract disturbances such as diarrhoea but these should be manageable with drug discontinuation. Of note, the higher incidence of diarrhoea in the Xoanacyl arm versus the active control arm in Study 304 is of some concern in a frail population.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
TSAT	LS mean (SE) CFB (week 12) Diff to pcb (95% CI)	%-p	10.2 (1.18)	-1.1 (1.20) 11.3 % (8.0, 14.7)	**SoE:** Week 12 diff to pcb (95% CI): Ferritin 77.5 ng/mL (56.2-98.7) Hgb 0.6 g/dL (0.4, 0.9) p<0.001	Study 204 (NDD)
Phosphate	LS mean (SE) CFB (week 12) Diff to pcb (95% CI)	mg/ dL	-0.7 (0.07)	-0.2 (0.07) -0.5 (-0.7, -0.3)	p<0.001	Study 204 (NDD)
Hgb response	Response rate week 12 Diff to pcb (95% CI)	%	52.1	19.133.0 (21.4, 44.6)	**SoE:** week 16 dif to pcb (95% CI**)** TSAT 18.4 % (14.6, 22.2) Ferritin 170.3 ng/mL (144.9, 195.7) Hgb 0.84 ng/mL (0.58, 1.10) p<0.001	Study 306 (NDD)
Phosphate (EU pep)	LS mean (SE) CFB (week 12)	mg/ dL	-2.03 (0.09) (2.00)	-2.17 (0.17) (2.18)	p=0.47 **SoE** Treatment ratio 1.02995% CI 0.959 to 1.104 Pre-spec NI margin: Upper bound <1.2	Study 304 (DD)
Hgb	LS mean (SE) CFB (week 52)	g/dL	-0.22 (0.08)	-0.52 (0.11)	**Unc:** study primarily designed to assess the effect on hyperphosphataemia No eligibility criteria for Hgb Eligibility criteria non optimal to assess TSAT and ferritin Diff. (95% CI) 0.30 (0.02-0.57) p=0.034 (Post Hoc analysis) week 52 Diff to pcb (95% CI) Ferritin 273.92 ng/mL (190.22, 357.61) TSAT 9.33 % (6.22, 12.44)	Study 304 (DD)
Unfavourable Effects						
GI-tract disturbances	Incidence of events, e.g. diarrhoea	%	75.3	61.7		NDD-pool
GI-tract disturbances	Incidence of events, e.g. diarrhoea	%	90.3 %			DD-pool
Hyperkalaemia	Incidence of hyperkalaemia	% >6.5m Eq/L	5.3	2.7		NDD-pool
Carbon dioxide/ bicarbonate levels	Change from baseline	mEq/L	+1.2	+0.1		Study 306 (NDD)
Hyper-glycaemia	Incidence of cases with >13.9 mmol/L	%	4.5	0.8		NDD-pool

Abbreviations: %-p: percentage point; CFB: change from baseline; Hgb: Haemoglobin, MO: major objection; NI: non inferiority; OC: other concern, pep: primary endpoint,
Notes:
Control: Placebo in Study 204 and Study 306; calcium acetate and/or sevelamer in Study304
Hgb response (Study 306) was defined as "the proportion of subjects achieving an increase in Hgb of ≥1.0 g/dL at any point between baseline and the end of the Randomised Period (Week 16)".
Phosphate (EU pep) (Study 304): a non-inferiority analysis at Week 12 of CFB in serum phosphate comparing Xoanacyl to sevelamer carbonate as single agent. Non-inferiority was claimed if the upper bound of the 2-sided 95% confidence interval for this ratio lay below 1.2.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The originally proposed indication for Xoanacyl was *Treatment of iron deficiency anaemia (IDA) in adult CKD patients with elevated serum phosphorus.*

In the response to the first LoQ, the following wording of the indication was proposed by the Applicant: *Treatment of concomitant iron deficiency and elevated serum phosphorous in adult patients with CKD*, which was partly agreed. However, based on the reasoning following below, the CHMP proposed the wording "*Treatment of concomitant elevated serum phosphorous and iron deficiency in adult patients with CKD*".

A relevant effect of Xoanacyl on hyperphosphataemia in subjects with CKD was shown for both the NDD- and the DD-populations in procedure EMEA/H/C/003776/0000 (Fexeric). The claim "*Treatment of elevated serum phosphorous"* for Xoanacyl is based on the same studies as in that procedure and is considered acceptable for both populations.

Evidence for a positive effect of Xoanacyl on iron deficiency anaemia in the non-dialysis dependent (NDD) population based on the results from Study 204 and Study 306 has been presented. These are generally acknowledged. Baseline TSAT and serum ferritin in these studies were below the levels where the *KDIGO 2012 guideline on anaemia* suggests iron administration in anaemic CKD patients if an increase in Hb level is desired. The reported increase of TSAT and ferritin in the studies supports a restoration of iron stores with treatment. Recently, a draft version of *the KDIGO 2025 Clinical practice guideline for anemia in chronic kidney disease (CKD)* has been published online, in which it is recommended that in people with CKD treated with iron, it is reasonable to withhold iron if ferritin ≥700 ng/ml (≥700 µg/l) or TSAT ≥40%. (Practice Point 2.2). The SmPC has been updated to reflect this to avoid the risk of iron overload.

Due to next to normal mean Hgb levels at baseline in Study 304 (patients on dialysis), this study population is not considered adequate to evaluate whether Xoanacyl treatment would indeed normalise Hgb in an anaemic DD-population.

The currently proposed indication has been updated to claim treatment of iron deficiency, i.e., also without anaemia. However, it could be argued that the study population of Study 304 is also not adequate for assessment of treatment of iron deficiency. Nonetheless, there is indirect support for an effect of Xoanacyl on iron stores in the DD-population since both ferritin and TSAT levels increased during treatment with Xoanacyl versus active control despite reduced administration of IV iron and ESA. This indicates that the iron released from the product at least to some extent is in fact taken up from the GI-tract which support that there is an effect of Xoanacyl on iron levels in the DD-population. However, it is acknowledged that the data is weak and that the effect size in the DD population is not known based on available data.
It is nonetheless considered that the results from Study 304 indicate that the use Xoanacyl as a phosphate binder in the DD-population should be limited to subjects with iron deficiency due to the risk of iron accumulation. A claim for "*Treatment of elevated serum phosphorous in subjects with iron deficiency*" could therefore be considered for the DD-population. However, to avoid different indications for the NDD- and DD-populations, the indication "*Treatment of concomitant elevated serum phosphorous and iron deficiency in adult patients with CKD*" was accepted. Monitoring of the effect as well as addition/reduction of other treatments for iron deficiency is crucial. Furthermore, it has been stated in the SmPC that the effect of Xoanacyl on iron deficiency has not been assessed in clinical trials in DD-subjects without concomitant treatment with intravenous iron and/or erythropoiesis-stimulating agent (ESA) as needed**.**

For all (co-) primary and secondary endpoints in the pivotal studies, a sensitivity analysis was performed. The results of the sensitivity analyses were similar to the primary analyses with the exception of serum phosphate, which was a secondary endpoint in study 306.

There was no pre-specified subgroup analysis for Study 204. In Study 306, a subgroup analysis for the primary endpoint (Hgb responders) showed no significant interactions of treatment with the characteristics of gender, age, race, baseline Hgb, or baseline CKD stage.

For Study 304, the Applicant presented a subgroup analysis for the US primary endpoint (serum phosphate Week 52-56) and for the characteristics of gender, age, race, and weight. The results of the subgroup analyses were generally consistent with those of the full analysis population (FAS).

The adverse effects pertain mainly to the GI-tract and could be of concern for the frailer part of the indicated population, in particular patients on dialysis. The adverse effects are nevertheless deemed possible to handle with SmPC texts (see SmPC for details).

3.7.2. Balance of benefits and risks

A benefit of Xoanacyl on hyperphosphataemia in both the NDD and the DD population is agreed.

Evidence for a positive effect of Xoanacyl on iron deficiency in the non-dialysis dependent (NDD) population based on the results from Study 204 and Study 306 has been presented.

Evidence for a positive effect of Xoanacyl on iron deficiency in the dialysis dependent (DD) population based on the results from Study 304 are weak and the effect size in the DD population is not known based on available data. Notwithstanding, there are indirect support for an effect on iron stores also in this population, hampering the use of Xoanacyl as phosphate binder in a non-iron deficient population. Therefore, a claim for "Treatment of iron deficiency" is therefore considered acceptable. Conclusions

The overall benefit/risk balance of Xoanacyl for "*Treatment of concomitant elevated serum phosphorous and iron deficiency in adult patients with CKD*" is positive, subject to the conditions stated in section 'Recommendations'.

NAS status cannot be granted since a similar product with the same active substance has already been approved in EU

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xoanacyl is favourable in the following indication(s):

"*Treatment of concomitant elevated serum phosphorous and iron deficiency in adult patients with CKD*"

The CHMP 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.

Other 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 marketing authorisation holder (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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Ferric citrate coordination complex is not to be qualified as a new active substance in itself as it is a constituent of a medicinal product previously authorised within the European Union although never commercialised within the European Union nor administered to any European patient.