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RESEARCH**

*APPLICATION NUMBER:*

**205874Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# Clinical Pharmacology/Biopharmaceutics Review

## Individual Study Review (ISR)

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PRODUCT (Generic Name):	KRX-0502 (Ferric Citrate)
NDA:	205-874
PRODUCT (Brand Name):	ZERENEX
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	(b) (4) mg tablets (210 mg iron)
INDICATION:	Control of serum phosphorus levels (b) (4) (b) (4) in patients with chronic kidney disease (CKD) on dialysis
NDA TYPE:	Standard
SUBMISSION DATE:	8/7/2013
SPONSOR:	Keryx Biopharmaceuticals, Inc.
REVIEWER:	Ju-Ping Lai, Ph.D.
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OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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## 1.1 IN VITRO STUDIES – DDI

### Amlodipine

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-amlodipine.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Amlodipine Besylate Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Amlodipine Besylate

**Objectives:** To assess the possible interactions between KRX-0502 and amlodipine by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Amlodipine besylate was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce amlodipine besylate solutions with a concentration of 0.025 mg/mL (pH 4.5 and pH 6.8 with phosphate) and 0.05 mg/mL (pH 4.5 and pH 6.8 without phosphate). These concentrations correspond to clinical relevant doses of 5 mg (for pH 4.5 and pH 6.8 with phosphate) or 10 mg (for pH 4.5 and pH 6.8 without phosphate) amlodipine besylate dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 2 hours, 4 hours and 6 hours. Samples were injected without dilution. Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections, except for T = 4 hours, which was injected once. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of amlodipine was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and amlodipine. The observed effects with presence of phosphate are considered as real life situation in fed condition.

#### Results

- Amlodipine besylate was not readily soluble. There were particles present in most of the media at the end of incubation with more solubility noted in absence of phosphate.
- Compared to concurrent controls, mean percent recoveries in the DDI solutions **without phosphate** at pH 4.5 and 6.8 were 96.7% and 88.2% at 2 hours, 93.5% and 83.4% at 4 hours, and increased to 99.5% and 90.3% at 6 hours.
- In the **presence of phosphate**, the percent recoveries compared to concurrent controls for the DDI solutions were 68.4 % and 61.5% at 2 hours, and increased to 70.0% and 66.5% at 4 hours, and to 90.0% and 86.3% at 6 hours at pH 4.5 and 6.8, respectively.

#### Reviewer's note:

- *The sponsor stated that the trend of increasing recoveries over time was due to the drug slowly dissolving in the solution which is not unreasonable.*
- *For the early time points at 2 and 4 hours, the recoveries were higher (lower binding) at the condition without the presence of phosphate when compared to the condition with the presence of phosphate. This finding is unexpected as presence of phosphate was expected*

*to compete with testing drugs for the binding to ferric citrate therefore should yield higher recoveries for testing drugs. This might be explained by the much lower dissolution of amlodipine in media with phosphate (~ 50% of that without the presence of phosphate).*

- *Data at 6 hours demonstrated no interaction liability at all conditions.*
- *Data at the worst case scenario (without phosphate) demonstrated no interaction liability at all conditions.*
- *To conservatively look at the data with the presence of phosphate, pH 4.5 is more clinically relevant with early time points where the bindings were ~31.6% and 30% at 2 and 4 hours respectively.*

**In vitro DDI results- Amlodipine- 2 hrs**

	2 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.04692	0.04538	<b>96.7</b>
pH 4.5, With Phosphate	0.02308	0.01579	<b>68.4</b>
pH 6.8, No Phosphate	0.05082	0.0448	<b>88.2</b>
pH 6.8, With Phosphate	0.02301	0.01414	<b>61.5</b>

**In vitro DDI results- Amlodipine- 4 hrs**

	4 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.04671	0.04372	<b>93.6</b>
pH 4.5, With Phosphate	0.02307	0.01614	<b>70.0</b>
pH 6.8, No Phosphate	0.05012	0.0418	<b>83.4</b>
pH 6.8, With Phosphate	0.02261	0.0153	<b>67.7</b>

**In vitro DDI results- Amlodipine- 6 hrs**

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.04659	0.04636	<b>99.5</b>
pH 4.5, With Phosphate	0.02287	0.02079	<b>90.9</b>
pH 6.8, No Phosphate	0.05079	0.04587	<b>90.3</b>
pH 6.8, With Phosphate	0.02267	0.01985	<b>87.6</b>

Source: reviewer summarized from study report mult-mod-info-amend-amlodipine, table 5-1 to 5-4, pages 25-28

**Assay**

System suitability, linearity, accuracy, precision, specificity (non-interference), PQL (Practical Quantitation Limit) and range were evaluated. The performance of the assay method during study sample analysis is acceptable.

**Conclusions:**

- The recoveries at 6 hours indicate that there was no interaction of amlodipine besylate with KRX-0502 (ferric citrate).

## Aspirin

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-aspirin.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Aspirin Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Aspirin

**Objectives:** To assess the possible interactions between KRX-0502 and aspirin by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Aspirin was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce aspirin solutions with a concentration of 3.25 mg/mL. This concentration corresponds to clinical relevant dose of 650 mg aspirin dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 2 hours, 4 hours and 6 hours. T=4 hours samples were directly stored at -20 °C and only T=2 and 6 hours were used for evaluation. These samples were diluted down to the 100 % nominal method concentration (0.325 mg/mL aspirin). Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of aspirin was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and aspirin. The observed effects with presence of phosphate are considered as real life situation in fed condition.

### Results

- The recoveries of aspirin in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 95.7 to 102.1 % indicating no interaction between aspirin and ferric citrate).

#### **In vitro DDI results- Aspirin- 2 hrs**

	2 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.36	0.412	<b>99.2</b>
pH 4.5, With Phosphate	0.362	0.408	<b>97.6</b>
pH 6.8, No Phosphate	0.347	0.332	<b>95.7</b>
pH 6.8, With Phosphate	0.345	0.333	<b>96.5</b>

#### **In vitro DDI results- Aspirin- 6 hrs**

	6 hours		

	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.369	0.424	99.4
pH 4.5, With Phosphate	0.374	0.422	97.9
pH 6.8, No Phosphate	0.358	0.344	96.1
pH 6.8, With Phosphate	0.358	0.345	96.4

Source: reviewer summarized from study report mult-mod-info-amend-aspirin, table 5-1 to 5-3, pages 24-26

#### Assay

System suitability, linearity, accuracy, precision, specificity (non-interference) and range were evaluated. The performance of the assay method during study sample analysis is acceptable.

#### Conclusions:

- The recoveries at 2 and 6 hours indicated that there was no interaction of aspirin with KRX-0502 (ferric citrate).

### Atorvastatin

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-atorvastatin.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Atorvastatin Calcium Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Atorvastatin Calcium

**Objectives:** To assess the possible interactions between KRX-0502 and Atorvastatin Calcium by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Atorvastatin calcium was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 6.8 in sufficient amounts to produce atorvastatin calcium solutions with a concentration of 0.011 mg/mL. This concentration corresponds to clinical relevant dose of 10 mg atorvastatin calcium dissolved in a volume of 900 mL. Experiments were conducted only at pH 6.8 because earlier experiments indicated that atorvastatin calcium was not soluble at pH 4.5. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 2 hours, 4 hours and 6 hours. T=4 hours samples were directly stored at -20 °C and only T=2 and 6 hours were used for evaluation. Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of atorvastatin was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and atorvastatin calcium. The observed effects with presence of phosphate are considered as real life situation in fed condition.

#### Results

- The recoveries of atorvastatin in all conditions (with and without phosphate and at pH 6.8)

ranged from 95.7 to 113.9 % indicating no interaction between atorvastatin and ferric citrate.

**In vitro DDI results- Atorvastatin- 2 hrs**

	2 hours		
	Control	DDI	Recovery (%)
pH 6.8, No Phosphate	0.0081	0.0092	<b>113.9</b>
pH 6.8, With Phosphate	0.0091	0.0094	<b>103.3</b>

**In vitro DDI results- Atorvastatin- 6 hrs**

	6 hours		
	Control	DDI	Recovery (%)
pH 6.8, No Phosphate	0.0095	0.0091	<b>95.7</b>
pH 6.8, With Phosphate	0.009	0.0092	<b>102.2</b>

Source: reviewer summarized from study report mult-mod-info-amend-atorvastatin, table 5-1 to 5-3, pages 23-25

**Assay**

System suitability, linearity, accuracy, precision, specificity (non-interference), range and practical quantitation limit were evaluated. The performance of the assay method during study sample analysis is acceptable.

**Conclusions:**

- The recoveries at 2 and 6 hours indicated that there was no interaction of atorvastatin with KRX-0502 (ferric citrate).

**Digoxin**

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-digoxin.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Digoxin Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Digoxin

**Objectives:** To assess the possible interactions between KRX-0502 and digoxin by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Digoxin was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce digoxin solutions with a concentration of 0.0025 mg/mL. This concentration corresponds to clinical relevant dose of 0.5 mg digoxin dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at 37 ± 2 °C for 6 hours. Aliquots were taken out of these solutions at 1 hour, 3 hours and 6 hours. T=3 hours samples were directly stored at -20 °C and only T=0, 1 and 6 hours were used for evaluation. Drug concentrations were determined by HPLC

analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of digoxin was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and digoxin. The observed effects with presence of phosphate are considered as real life situation in fed condition.

**Results**

- The recoveries of digoxin in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 99.6 to 110.1 % indicating no interaction between digoxin and ferric citrate).

**In vitro DDI results- Digoxin- 1 hr**

	1 hour		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.001935	0.002031	<b>105.0</b>
pH 4.5, With Phosphate	0.00195	0.001943	<b>99.6</b>
pH 6.8, No Phosphate	0.001903	0.001957	<b>102.8</b>
pH 6.8, With Phosphate	0.001825	0.001916	<b>105.0</b>

**In vitro DDI results- Digoxin- 6 hrs**

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.001929	0.002026	<b>105.0</b>
pH 4.5, With Phosphate	0.001903	0.001935	<b>101.7</b>
pH 6.8, No Phosphate	0.001771	0.001898	<b>107.2</b>
pH 6.8, With Phosphate	0.001739	0.001914	<b>110.1</b>

Source: reviewer summarized from study report mult-mod-info-amend-digoxin, table 5-1 to 5-3, pages 23-25

**Assay**

System suitability, linearity, accuracy, precision, specificity (non-interference), range and practical quantitation limit (PQL) were evaluated. The performance of the assay method during study sample analysis is acceptable.

**Conclusions:**

- The recoveries at 1 and 6 hours indicated that there was no interaction of digoxin with KRX-0502 (ferric citrate).

**Doxycycline**

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-doxycycline.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Doxycycline Hyclate

**Objectives:** To assess the possible interactions between KRX-0502 and doxycycline by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Doxycycline hyclate was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce doxycycline hyclate solutions with a concentration of 0.5 mg/mL. This concentration corresponds to clinical relevant dose of 100 mg doxycycline hyclate dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 1 hour, 3 hours and 6 hours. T = 3 hours samples were directly stored at -20 °C and only T = 0, 1 and 6 hours were used for evaluation. Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of doxycycline was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and doxycycline hyclate. The observed effects with presence of phosphate are considered as real life situation in fed condition.

**Results**

- The recoveries of doxycycline in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 1.5 to 32.2 % indicating that there was an interaction between doxycycline and ferric citrate.

**In vitro DDI results- Doxycycline- 1 hr**

	1 hour		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.4965	0.0588	<b>11.8</b>
pH 4.5, With Phosphate	0.4941	0.1589	<b>32.2</b>
pH 6.8, No Phosphate	0.477	0.0176	<b>3.7</b>
pH 6.8, With Phosphate	0.4856	0.1324	<b>27.3</b>

**In vitro DDI results- Doxycycline- 6 hrs**

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.4953	0.0283	<b>5.7</b>
pH 4.5, With Phosphate	0.4916	0.1501	<b>30.5</b>
pH 6.8, No Phosphate	0.4768	0.0072	<b>1.5</b>
pH 6.8, With Phosphate	0.4836	0.055	<b>11.4</b>

Source: reviewer summarized from study report mult-mod-info-amend-doxycycline, table 4-1 to 4-3, pages 11-13

**Assay**

System suitability, accuracy, precision and specificity (non-interference) were evaluated. The

performance of the assay method during study sample analysis is acceptable.

**Conclusions:**

- The recoveries at 1 and 6 hours indicated that there was an interaction between doxycycline and KRX-0502 (ferric citrate).

**Fluvastatin**

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-fluvastatin.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Fluvastatin Sodium Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Fluvastatin Sodium

**Objectives:** To assess the possible interactions between KRX-0502 and Fluvastatin Sodium by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Fluvastatin sodium was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 6.8 in sufficient amounts to produce fluvastatin sodium solutions with a concentration of 0.4 mg/mL. This concentration corresponds to clinical relevant dose of 80 mg fluvastatin sodium dissolved in a volume of 200 mL. Experiments were conducted only at pH 6.8 because fluvastatin sodium was not soluble at pH 4.5. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 2 hours, 4 hours and 6 hours. Aliquots from all the samples were stored at -20 °C. Frozen aliquots of T=2 and 6 hours were thawed and used for evaluation. Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of fluvastatin was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and fluvastatin sodium. The observed effects with presence of phosphate are considered as real life situation in fed condition.

**Results**

- The recoveries of fluvastatin in all conditions (with and without phosphate and at pH 6.8) ranged from 98.4 % to 100.7 % indicating no interaction between fluvastatin and ferric citrate.

**In vitro DDI results- Fluvastatin- 2 hrs**

	2 hours		
	Control	DDI	Recovery (%)
pH 6.8, No Phosphate	0.377749	0.374696	99.2
pH 6.8, With Phosphate	0.37535	0.369279	98.4

**In vitro DDI results- Fluvastatin- 6 hrs**

	6 hours		
	Control	DDI	Recovery (%)
pH 6.8, No Phosphate	0.37286	0.376572	<b>101.0</b>
pH 6.8, With Phosphate	0.376768	0.377503	<b>100.2</b>

Source: reviewer summarized from study report mult-mod-info-amend-fluvastatin, table 5-1 to 5-3, pages 23-25

**Assay**

System suitability, linearity, accuracy, precision, specificity (non-interference) and range were evaluated. The performance of the assay method during study sample analysis is acceptable.

**Conclusions:**

- The recoveries at 2 and 6 hours indicated that there was no interaction of fluvastatin with KRX-0502 (ferric citrate).

**Levofloxacin**

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-levofloxacin.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Levofloxacin HCl

**Objectives:** To assess the possible interactions between KRX-0502 and levofloxacin by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Levofloxacin HCl was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce levofloxacin HCl solutions with a concentration of 3.75 mg/mL. This concentration corresponds to clinical relevant dose of 750 mg levofloxacin HCl dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 1 hour, 3 hours and 6 hours. T = 3 hours samples were directly stored at -20 °C and only T = 0, 1 and 6 hours were used for evaluation. These samples were diluted down to the 100 % nominal method concentration (1.0 mg/mL levofloxacin HCl). Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of levofloxacin was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and levofloxacin. The observed effects with presence of phosphate are considered as real life situation in fed condition.

**Results**

- The recoveries of levofloxacin in all conditions (with and without phosphate and at pH 4.5 and

6.8) ranged from 89.1 to 98.7 % indicating no interaction between levofloxacin and ferric citrate.

**In vitro DDI results- Levofloxacin- 1 hr**

	1 hour		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.946	0.920	<b>97.3</b>
pH 4.5, With Phosphate	0.963	0.858	<b>89.1</b>
pH 6.8, No Phosphate	0.952	0.939	<b>98.6</b>
pH 6.8, With Phosphate	0.953	0.941	<b>98.7</b>

**In vitro DDI results- Levofloxacin- 6 hrs**

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.951	0.922	<b>97.0</b>
pH 4.5, With Phosphate	0.964	0.905	<b>93.9</b>
pH 6.8, No Phosphate	0.957	0.935	<b>97.7</b>
pH 6.8, With Phosphate	0.967	0.935	<b>96.7</b>

Source: reviewer summarized from study report mult-mod-info-amend-levofloxacin, table 4-1 to 4-3, pages 12-14

**Assay**

System suitability, accuracy, precision, specificity (non-interference) was evaluated. The performance of the assay method during study sample analysis is acceptable.

**Conclusions:**

- The recoveries at 1 and 6 hours indicated that there was no interaction of levofloxacin with KRX-0502 (ferric citrate).

**Metoprolol**

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-metoprolol.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Metoprolol Tartrate Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Metoprolol Tartrate

**Objectives:** To assess the possible interactions between KRX-0502 and metoprolol by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Metoprolol tartrate was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce metoprolol tartrate solutions with a concentration of 1.0 mg/mL. This concentration corresponds to clinical relevant dose of 200 mg metoprolol tartrate dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and

DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 1 hour, 3 hours and 6 hours. T = 3 hours samples were directly stored at -20 °C and only T = 0, 1 and 6 hours were used for evaluation. Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of metoprolol was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and metoprolol. The observed effects with presence of phosphate are considered as real life situation in fed condition.

### Results

- The recoveries of metoprolol in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 96.1 to 98.3 % indicating no interaction between metoprolol and ferric citrate.

#### In vitro DDI results- Metoprolol- 1 hr

	1 hour		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.992362	0.96886	<b>97.6</b>
pH 4.5, With Phosphate	1.003346	0.983114	<b>98.0</b>
pH 6.8, No Phosphate	1.009884	0.970913	<b>96.1</b>
pH 6.8, With Phosphate	1.007888	0.980716	<b>97.3</b>

#### In vitro DDI results- Metoprolol- 6 hrs

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.985343	0.966307	<b>98.1</b>
pH 4.5, With Phosphate	0.995938	0.979063	<b>98.3</b>
pH 6.8, No Phosphate	1.002856	0.968686	<b>96.6</b>
pH 6.8, With Phosphate	1.002351	0.978808	<b>97.7</b>

Source: reviewer summarized from study report mult-mod-info-amend-metoprolol, table 5-1 to 5-3, pages 24-26

#### Assay

System suitability, linearity, accuracy, precision, specificity (non-interference) and range were evaluated. The performance of the assay method during study sample analysis is acceptable.

#### Conclusions:

- The recoveries at 1 and 6 hours indicated that there was no interaction of metoprolol with KRX-0502 (ferric citrate).

## Pravastatin

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-pravastatin.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Pravastatin Sodium Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Pravastatin Sodium

**Objectives:** To assess the possible interactions between KRX-0502 and pravastatin sodium by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Pravastatin sodium was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce pravastatin sodium solutions with a concentration of 0.4 mg/mL. This concentration corresponds to clinical relevant dose of 80 mg pravastatin sodium dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 1 hour, 3 hours and 6 hours. T = 3 hours samples were directly stored at -20 °C and only T = 0, 1 and 6 hours were used for evaluation. These samples were diluted to 0.2 mg/mL. Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of pravastatin was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and pravastatin sodium. The observed effects with presence of phosphate are considered as real life situation in fed condition.

## Results

- The recoveries of pravastatin in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 96.3 to 99.2 % indicating no interaction between pravastatin and ferric citrate.

### In vitro DDI results- Pravastatin- 1 hr

	1 hour		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.1771	0.1732	97.8
pH 4.5, With Phosphate	0.1765	0.171	96.9
pH 6.8, No Phosphate	0.1838	0.1823	99.2
pH 6.8, With Phosphate	0.1859	0.1835	98.7

### In vitro DDI results- Pravastatin- 6 hrs

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.1694	0.1631	96.3
pH 4.5, With Phosphate	0.1685	0.1624	96.4

pH 6.8, No Phosphate	0.1857	0.1818	<b>97.9</b>
pH 6.8, With Phosphate	0.1861	0.1835	<b>98.6</b>

Source: reviewer summarized from study report mult-mod-info-amend-pravastatin, table 5-1 to 5-3, pages 2-27

#### Assay

System suitability, linearity, accuracy, precision, specificity (non-interference), range and Practical Quantitation Limit (PQL) were evaluated. The performance of the assay method during study sample analysis is acceptable.

#### Conclusions:

- The recoveries at 1 and 6 hours indicated that there was no interaction of pravastatin with KRX-0502 (ferric citrate).

## Propranolol

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-propranolol.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Propranolol HCl Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Propranolol HCl

**Objectives:** To assess the possible interactions between KRX-0502 and propranolol by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Propranolol HCl was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce propranolol HCl solutions with a concentration of 0.4 mg/mL. This concentration corresponds to clinical relevant dose of 80 mg propranolol HCl dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 1 hour, 3 hours and 6 hours. T = 3 hours samples were directly stored at -20 °C and only T = 0, 1 and 6 hours were used for evaluation. These samples were diluted down to the 100 % nominal method concentration (0.02 mg/mL propranolol HCl). Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of propranolol was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and propranolol HCl. The observed effects with presence of phosphate are considered as real life situation in fed condition.

#### Results

- The recoveries of propranolol in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 94.6 to 101.5 % indicating no interaction between propranolol and ferric citrate.

**In vitro DDI results- Propranolol- 1 hr**

	1 hour		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.0204	0.0207	<b>101.5</b>
pH 4.5, With Phosphate	0.0208	0.0197	<b>94.7</b>
pH 6.8, No Phosphate	0.0197	0.0200	<b>101.5</b>
pH 6.8, With Phosphate	0.0197	0.0197	<b>100.0</b>

**In vitro DDI results- Propranolol- 6 hrs**

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.0204	0.0200	<b>98.0</b>
pH 4.5, With Phosphate	0.0205	0.0205	<b>100.0</b>
pH 6.8, No Phosphate	0.0198	0.0198	<b>100.0</b>
pH 6.8, With Phosphate	0.0199	0.0199	<b>100.0</b>

Source: reviewer summarized from study report mult-mod-info-amend-propranolol, table 5-1 to 5-3, pages 24-26

**Assay**

System suitability, linearity, accuracy, precision, specificity (non-interference) and range were evaluated. The performance of the assay method during study sample analysis is acceptable.

**Conclusions:**

- The recoveries at 1 and 6 hours indicated that there was no interaction of propranolol with KRX-0502 (ferric citrate).

**Warfarin**

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-warfarin.pdf

**Title:** *In-vitro* Drug-Drug Interaction Time Course Study with KRX-0502 (Ferric Citrate) and Warfarin Sodium Together with Qualification of the Reversed Phase High Performance Liquid Chromatographic (RP-HPLC) Method for Determining the Concentration of Warfarin Sodium

**Objectives:** To assess the possible interactions between KRX-0502 and warfarin by measuring the remaining concentration of the drug in aqueous solution with and without phosphate obtained after incubation with KRX-0502

**Study Design:** Warfarin sodium was added to solutions of 10 mg/mL ferric citrate, with and without 2 mg/mL phosphate, buffered at pH 4.5 and 6.8 in sufficient amounts to produce warfarin sodium solutions with a concentration of 0.0025 mg/mL at pH 4.5 and 0.05 mg/mL at pH 6.8. These concentrations corresponds to clinical relevant doses of 0.5 mg (for pH 4.5) or 10 mg (for pH 6.8) warfarin sodium, each dissolved in a volume of 200 mL. As controls, same media were prepared without presence of ferric citrate with the same concentration of the drug as DDI at the corresponding pH. Warfarin sodium was added to the pH 6.8 solutions as a powder, and was

diluted into the pH 4.5 solutions from a 0.5 mg/mL methanol stock solution due to lower solubility at pH 4.5 in the presence phosphate. Controls were prepared once and DDI solutions were prepared in duplicate. All solutions were incubated at  $37 \pm 2$  °C for 6 hours. Aliquots were taken out of these solutions at 1 hour, 3 hours and 6 hours. T = 3 hours samples were directly stored at -20 °C and only T = 0, 1 and 6 hours were used for evaluation. The pH 6.8 DDI and control samples, with and without phosphate, were diluted down to the 100 % nominal method concentration (0.0125 mg/mL warfarin sodium). The pH 4.5 samples were injected neat. Drug concentrations were determined by HPLC analysis. Each control and DDI solution aliquot was evaluated in duplicate injections. Percent recovery was calculated as “% Recovery based on the controls”.

Quantification of warfarin was performed by HPLC with UV detection.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and warfarin sodium. The observed effects with presence of phosphate are considered as real life situation in fed condition.

### Results

- The recoveries of warfarin in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 91.3 to 98.2 % indicating no interaction between warfarin and ferric citrate.

#### In vitro DDI results- Warfarin-1 hr

	1 hour		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.0023	0.0021	<b>91.3</b>
pH 4.5, With Phosphate	0.0023	0.0021	<b>91.3</b>
pH 6.8, No Phosphate	0.0109	0.0107	<b>98.2</b>
pH 6.8, With Phosphate	0.0111	0.0109	<b>98.2</b>

#### In vitro DDI results-Warfarin-6hrs

	6 hours		
	Control	DDI	Recovery (%)
pH 4.5, No Phosphate	0.0023	0.0022	<b>95.7</b>
pH 4.5, With Phosphate	0.0023	0.0021	<b>91.3</b>
pH 6.8, No Phosphate	0.0109	0.0107	<b>98.2</b>
pH 6.8, With Phosphate	0.0111	0.0109	<b>98.2</b>

Source: reviewer summarized from study report mult-mod-info-amend-warfarin, table 5-1 to 5-3, pages 26-28

#### Assay

System suitability, linearity, accuracy, precision, specificity (non-interference), Practical Quantitation Limit (PQL) and range were evaluated. The performance of the assay method during study sample analysis is acceptable.

#### Conclusions:

- The recoveries at 1 and 6 hours indicated that there was no interaction of warfarin with KRX-

0502 (ferric citrate).

### Six Drugs

**EDR Link:** \\cdsesub1\evsprod\nda205874\0048\m1\us\111-info-amend\mult-mod-info-amend-ddi-wil.pdf

**Title:** Qualification of HPLC Analytical Methods to Assess KRX-0502-Analyte Drug-Drug Interactions

**Objectives:** To evaluate the ability of 6 test drugs to bind to KRX-0502 (ferric citrate) following incubations for up to 6 hours at approximately 37°C in the presence or absence of 2 mg/mL phosphate at pH 4.5 and pH 6.8.

**Study Design:** The general approach was to separately incubate the six test drugs at same conditions at approximately 37°C with KRX-0502 (ferric citrate) drug substance for various times (0, 1, 3 and 6 hours) at pH 4.5 and/or pH 6.8, in the presence or absence of 2 mg/mL phosphate, and then centrifuge to remove any precipitate, and quantitate the test drug (calcitriol, clopidogrel bisulfate, doxercalciferol, enalapril maleate, sitagliptin phosphate monohydrate, or warfarin sodium) in the supernatant using HPLC, and compare the concentration to a control prepared without ferric citrate, and incubated for the same time, as well as to baseline (T = 0) values. The concentrations tested correspond to clinical relevant dose for each drug.

Different HPLC based methods using UV absorbance detection for the determination of drug-ferric citrate interactions were utilized in this study.

The observed effects without presence of phosphate are considered as maximum interactions between ferric citrate and testing drugs. The observed effects with presence of phosphate are considered as real life situation in fed condition.

#### Results

- The recoveries of all testing drugs in all conditions (with and without phosphate and at pH 4.5 and 6.8) ranged from 88.51 to 102.91 % indicating no interaction between testing drugs and ferric citrate).

Drug Candidate	Buffer	Concentration Ratio over time (in %)			
		0 hr	1 hr	3 hr	6 hr
Calcitriol	1	100.49	101.87	99.69	99.19
	2	102.91	101.74	99.22	99.43
	3	97.99	101.73	100.87	98.74
	4	99.47	98.85	98.83	99.80
Doxercalciferol	1	96.55	94.27	92.59	94.08
	2	94.96	92.26	93.77	95.03
	3	93.72	91.80	94.04	93.52
	4	95.34	93.29	94.55	91.66
Warfarin Sodium	1	98.34	99.36	99.30	97.75
	2	96.34	97.12	97.68	96.58
	3	89.91	92.14	89.81	90.01
	4	92.59	91.85	88.60	90.05
Sitagliptin Phosphate	1	100.99	101.19	100.20	99.48
	2	99.97	100.44	100.11	97.95
	3	99.95	99.83	100.02	99.94
	4	100.07	98.91	100.08	98.15
Clopidogrel Bisulfate	1	99.15	99.10	99.53	96.94
	2	99.07	99.74	100.21	98.52
	3	99.71	99.68	99.74	99.22
	4	100.21	99.59	99.06	100.40
Enalapril Maleate	1	90.61	90.95	89.43	90.78
	2	90.08	90.80	89.35	90.59
	3	89.16	89.11	88.51	90.03
	4	90.63	92.35	90.85	90.55

1 = Sodium acetate buffer, pH 4.5

2 = Sodium acetate buffer with 2 mg/mL phosphate, pH 4.5

3 = Bis tris propane buffer, pH 6.8

4 = Bis tris propane buffer with 2 mg/mL phosphate, pH 6.8

Source: study report mult-mod-info-amend-ddi-wil, pages 17

### Assay

For all the different test drugs, method development was carried out to select an assay which was replicable and did not interfere with the buffer and KRX-0502. Assay specificity/selectivity, precision, accuracy and stability for each of the test drugs in calibration standards stored at room temperature for 24 hours were assessed. In addition, solubility for each of the test drugs was also assessed at a specific concentration that was within the range of the calibration curve. The performance of the assay method during study sample analysis is acceptable.

### Conclusions:

- The recoveries at up to 6 hours indicated that there were no meaningful drug-drug interactions with ferric citrate (KRX-0502) and calcitriol, doxercalciferol, sitagliptin phosphate, warfarin sodium, clopidogrel bisulfate, and enalapril maleate *in vitro*.

## 1.2 PHARMACOKINETICS – IRON ABSORPTION

<b>Study Report #</b> KRX-0502-201	<b>Study period</b> 05/28/08-12/11/08
<p><b>Title:</b> A Safety and Tolerability Study of Zerenex (ferric citrate) in Patients with End-Stage Renal Disease (ESRD)</p> <p><b>EDR Link:</b> \\cdsesub1\evsprod\nda205874\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hyperphosphatemia\5352-stud-rep-uncontr\krx-0502-201\krx-0502-201-body.pdf</p>	
<p><b>Primary Objectives</b></p> <p>To assess the tolerability and safety of KRX-0502 (ferric citrate) ranging from 1 capsule/day to 30 capsules/day (<math>\approx 11.3</math> g/day) in patients with end-stage renal disease (ESRD).</p> <p><i>Reviewer's note: This study was submitted to support the extent of iron absorption; hence this review would only focus on the changes of iron parameters.</i></p>	
<p><b>Study Design:</b> This trial was a multicenter, non-blinded, exploratory study in patients with ESRD on thrice-weekly hemodialysis. Approximately 55 patients were initiated on KRX-0502 (ferric citrate). To be initiated on study drug, the test results from Screening (Visit -1, Week -2) must have included a ferritin &lt;1000 micrograms/L, a Transferrin iron saturation (TSAT) &lt;50%, and a serum phosphorus <math>\geq 2.5</math> mg/dL (Part 1) or <math>\geq 3.5</math> mg/dL (Part 2). There was no washout period in this study. The phosphate binder(s) were switched immediately to KRX-0502.</p> <p>KRX-0502 was supplied as 375 mg capsules. All patients were started either at 12 capsules/day (<math>\approx 4.5</math> g/day) in Part 1 (n=34) or 16 capsules/day (<math>\approx 6.0</math> g/day) in Part 2 (n= 21) for one week and the dose was adjusted based on weekly serum phosphate levels. The maximum number of KRX-0502 capsules per day was to be 30 (<math>\approx 11.3</math> g/day).</p> <p>If the patients required greater than 30 capsules per day of KRX-0502, or if the serum phosphorus concentration was &gt;11mg/dL confirmed on two consecutive visits on any dose of study drug, this was defined as a treatment failure.</p> <p>Use of Vitamin D (and its analogs) and Sensipar (cinacalcet) were administered at the discretion of the local physicians. Calcium supplements could have been given but not concurrently with food and at the discretion of the investigators or treating physicians. It was recommended that calcium supplements be taken at bedtime or two hours or more prior to or after a patient's meal or snack. IV iron therapy was permitted in patients when ferritin was &lt;500 micrograms/L, TSAT was &lt;25%, or at the discretion of the treating physicians.</p>	
<p><b>Study medication</b></p> <p>KRX-0502 (ferric citrate) was supplied as a 375 mg capsule. The capsules were manufactured in compliance with Good Manufacturing Practice (cGMP) at [REDACTED] (b) (4)</p>	
<p><b>Sampling schedules:</b></p> <p><b>Serum phosphate and serum calcium:</b> Screening, Baseline, Weeks 1, 2, 3 and 4</p>	

**Iron parameters** (serum iron, total iron binding capacity (IBC), ferritin, and transferrin saturation percentage): Screening, Baseline and Week 4

### Data Analysis Methods

This trial was exploratory in nature and was intended to provide additional tolerability and safety data on KRX-0502 (ferric citrate). The objective of the data analysis was primarily descriptive. Statistical significance tests could have been performed, but it was not a primary goal of the trial to reach definitive statistical conclusions. The main analyses were done on Intent-to-treat (ITT) population.

### Study population

Variable		Units	
Age	Mean (SD)	Year	53.46 (11.48)
Gender	Frequency	N (%)	23 (41.8) Female 32 (58.2) Male
Race	Frequency	N (%)	36 (65.4) Black 14 (25.5) White 5 (9.1) Other
Ethnicity	Frequency	N (%)	12 (21.8) Hispanic 43 (78.2) Non-Hispanic

Source: Study report krx-0502-201, Table 9, Page 43

### Results:

#### Serum Phosphorus levels

- Serum phosphorus decreased from 5.9 mg/dL prior to the immediate switch to ferric citrate to 5.4 mg/dL at Week 4.

#### Iron Parameters (Serum iron, Ferritin, Transferrin Saturation Percentage, Total Iron Binding Capacity)

- Serum iron, ferritin, and TSAT levels increased, and Total Iron Binding Capacity (TIBC) levels decreased, in both the iron-supplemented and non-iron-supplemented groups. Only the decrease in TIBC in the non-iron-supplemented group, the increase in ferritin in the iron-supplemented group, and the increases in TSAT in both iron-supplemented and non-iron-supplemented groups were statistically significant.
- The increase in TSAT, the measure considered most closely to reflect circulating iron available for erythropoiesis, was similar in the 2 groups (absolute change of 3% with no IV iron versus 5.7% with IV iron supplementation). This confirms that iron is absorbed to a clinically meaningful extent following KRX-0502 administration.

**Table 5: Iron-related Laboratory Test Results (Study-201)**

	Group	Mean		Change from Baseline at EOT <sup>a</sup> Mean (%)
		Baseline	Week 4	
Serum iron (µg/dL)	IV iron supplementation	67.5	76.8	9.3 (13.8%)
	No IV iron supplementation	69.8	74.1	4.3 (6.2%)
Ferritin (ng/mL)	IV iron supplementation	513.9	586.7	72.8 (14.2%) <sup>b</sup>
	No IV iron supplementation	613.6	627.2	13.6 (2.2%)
TIBC (µg/dL)	IV iron supplementation	226.6	220.5	-6.1 (-2.7%)
	No IV iron supplementation	229.2	214.0	-15.2 (-6.6%) <sup>b</sup>
TSAT (%)	IV iron supplementation	30.1	35.8	5.7 (18.9%) <sup>b</sup>
	No IV iron supplementation	30.7	35.0	4.3 (14.0%) <sup>b</sup>

Source: Study 201, Table 16 and Table 17.

<sup>a</sup> Percent change from baseline is calculated as follows: [(last mean value – baseline mean value) / baseline mean value] × 100.

<sup>b</sup> Significant difference between baseline and EOT (p<0.05).

EOT=end of treatment; IV=intravenous; TIBC=total iron binding capacity; TSAT=transferrin iron saturation.

Source: Summary of Clinical Pharmacology, Table 5, Page 13

### Safety

Death: **None**

- There were four serious adverse events (SAE) reported (liver infection, methicillin – susceptible staphylococcus aureus bacteremia, suicide attempt and worsened congestive heart failure). All SAEs were considered unrelated to study drug.
- Seven patients did not complete 28 days of treatment with KRX-0502; six were due to an adverse event and one was due to difficulty swallowing the capsules. All of the adverse events were related to the GI system.

### Conclusion

- Serum phosphorus levels were maintained after switching to KRX-0502 for 4 weeks.
- Iron absorption was reflected by various degrees of changes on iron parameters, serum iron, ferritin, TSAT and TIBC.

<b>Study Report #</b> KRX-0502-202	<b>Study period</b> 01/25/10-04/29/10
<p><b>Title:</b> A 6-Week Feasibility Trial of a New Formulation of KRX-0502 (Ferric Citrate) in Patients with End-Stage Renal Disease (ESRD)</p> <p><b>EDR Link</b> \\cdsub1\evsprod\nda205874\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\krx-0502-202\krx-0502-202-body.pdf</p>	
<p><b>Primary Objectives</b></p> <p>To determine the potential efficacy as a dietary phosphate binder and tolerability of KRX-0502 (ferric citrate) in controlling and managing serum phosphorus levels in subjects with ESRD. The primary outcome of this trial was the change in serum phosphorus from baseline to end of treatment after a four week treatment period.</p> <p><i>Reviewer's note: This study was an exploratory study for the efficacy for 1 gram caplet of ferric citrate. However, this study also intended to support the extent of iron absorption. Since efficacy of ferric citrate was evaluated by pivotal studies, this review would only focus on the changes of iron parameters.</i></p>	
<p><b>Study Design:</b> This was a multi-center, non-blinded, study with a two-week washout period immediately followed by a six-week treatment period in subjects with ESRD on thrice weekly hemodialysis. Approximately 24 subjects (twelve diabetic and twelve non-diabetic subjects) were planned to be enrolled and treated with 1gram caplets of ferric citrate. The study consisted of five periods: Screening, Washout, Study Drug Initiation, Treatment, and Final Visit.</p> <p>All subjects initiated on ferric citrate were started with a fixed dose of KRX-0502 of 6 caplets per day (approximately 1,260 mg of ferric iron as ferric citrate). Subjects were titrated at Weeks 1, 2, and 3. The maximum number of KRX-0502 caplets was 12 g/day. Subjects were to take ferric citrate orally with meals or snacks or within one hour after their meals or snacks. Subjects were instructed not to take the study drug if greater than one hour has passed since the ingestion of their meals or snacks.</p>	
<p><b>Study medication</b></p> <p>KRX-0502 (ferric citrate) was supplied as one caplet of ferric citrate containing approximately 210 mg of ferric iron as ferric citrate.</p>	
<p><b>Sampling schedules:</b></p> <p><b>Serum phosphate and serum calcium:</b> Screening, washout, baseline, Weeks 1, 2, 3 and 4</p> <p><b>Iron parameters</b> (serum iron, total IBC, ferritin, and transferrin saturation percentage): Screening, baseline and Week 4</p>	
<p><b>Data Analysis Methods</b></p> <p><b>Efficacy:</b> This study was exploratory in nature and was intended to be a Phase 2 study to assess the tolerability and safety of 1 gram caplets of ferric citrate. The objective of the efficacy data analysis was primarily descriptive. Analyses were conducted on an intention-to-treat (ITT) population. The ITT population was defined as any subject that received study drug and had a baseline serum phosphorus level.</p> <p><b>Safety:</b> Recording and monitoring adverse events and obtaining sequential blood chemistries and</p>	

hematology parameters were used to assess safety. Rates of adverse events and changes in laboratory parameters were summarized. The Safety Population was all subjects that received ferric citrate.

### Study population

Parameters	N=22
Gender M/F/Missing (n)	14/7/1
Age in years (mean ± SD)	55 ± 0.8
Race n (%)	
Caucasian	19 (86.4%)
Indian-Far East <sup>1</sup>	1 (4.5%)
Arab <sup>1</sup>	1 (4.5%)
Missing	1 (4.5%)

N, n = number of subjects SD=standard deviation  
1-as documented on the case report form  
See Data Listing 1.

Source: Study report krx-0502-202, Table 1, Page 6

### Results:

#### Serum Phosphorus levels

- Ferric citrate decreased serum phosphorus from 7.4 mg/dL at baseline to 5.8 mg/dL at Week 4.

**Table 2: Change in Serum Phosphorus (mg/dL) over Time**

	Visit Number	N	Mean ± SD	Min, Max
Screening	0	22	5.5 ± 1.3	3.3, 8.8
Washout Period	1	15	5.9 ± 1.2	3.4, 7.6
Washout Period	2	6	5.5 ± 1.1	3.5, 6.6
End of Washout Period	3	18	7.4 ± 1.3	5.9, 10.8
Week 1	4	19	6.1 ± 1.6	3.4, 9.3
Week 2	5	16	6.2 ± 1.8	3.2, 10.7
Week 3	6	14	6.2 ± 1.7	3.6, 9.6
Week 4 (End of Treatment)	7	19	5.8 ± 1.3	3.7, 9.1

N, n = number of subjects; SD = standard deviation; Min = minimum value; Max = maximum value  
See Data Listing 2 for individual chemistry results

Results from Site 001 were converted from SI units to conventional units (dividing by a factor of 0.323; reference: AMA Manual of Style, SI conversion table)

Source: Study report krx-0502-202, Table 2, Page 6

#### Iron Parameters (Serum iron, Ferritin, Transferrin Saturation Percentage, Total Iron Binding Capacity)

- After 4 weeks of treatment with KRX-0502, mean serum iron increased by 70.2% (p<0.01) and mean TSAT levels increased by 36.3% (from 22.84% to 31.13%; NS). Mean ferritin and TIBC levels at Week 4 were not significantly different from baseline.

**Table 6: Iron-related Laboratory Test Results (Study 202)**

	Mean (SD)		
	Baseline	Week 4	Change from Baseline at EOT <sup>a</sup> Mean (%)
Serum iron (µg/dL)	57.67 (20.0)	98.15 (62.2)	40.48 (70.2%) <sup>b</sup>
Ferritin (ng/mL)	424.75 (301.87)	430.07 (313.0)	5.32 (1.3%)
TIBC (µg/dL)	235.78 (37.7)	229.19 (38.8)	-6.59 (-2.8%)
TSAT (%)	22.84 (7.9)	31.13 (11.3)	8.29 (36.3%)

Source: Study 202, Appendix 16.2.8.

Results displayed were calculated for observed cases in which values were available for both baseline (Visit 3) and Week 4 / End of Study (Visit 7).

<sup>a</sup> Percent change from baseline is calculated as follows: [(last mean value - baseline mean value) / baseline mean value] × 100.

<sup>b</sup> p<0.01 Wilcoxon matched pairs signed-ranks test.

EOT=end of treatment; SD=standard deviation; TIBC=total iron binding capacity; TSAT=transferrin iron saturation.

Source: Summary of Clinical Pharmacology, Table 6, Page 14

## Safety

### Death: None

- There was one severe adverse event report (clotted A-V fistula recurrent) which was unrelated to the administration of ferric citrate.
- Four patients discontinued due to AEs: 1) a 36 year-old female experienced diffuse rash and itch. These were mild to moderate in intensity and considered related to ferric citrate by Principle Investigator; 2) a 64 year-old male experienced nausea, odor of ferric citrate, hand dysaesthesia and a strange feeling in the head. These were mild in intensity and considered unrelated to ferric citrate; 3) a 55 year-old male experienced abdominal pain and diarrhea. These were moderate in intensity and were considered related to ferric citrate and 4) a 34 year-old female experienced abdominal pain and exacerbation of constipation. These were moderate in intensity and considered related to ferric citrate. The AEs are in line with what was observed in the Phase III trial.

## Conclusion

- Mean serum iron and TSAT levels increased by 70.2% and 36.3%, respectively, at week 4. Mean ferritin and TIBC levels at Week 4 were not significantly different from baseline.

### 1.3 PHARMACODYNAMICS – SERUM PHOSPHATE

#### DOSE-RESPONSE RELATIONSHIP

<b>Study Report #</b> KRX-0502-305	<b>Study period</b> 206/01/10-11/19/10
<b>Title:</b> A 4-Week Dose-Ranging and Efficacy Study of KRX-0502 (Ferric Citrate) in Patients with End-Stage Renal Disease (ESRD) Following a Two-Week Washout Period	
<b>EDR Link:</b> \\cdsesub1\evsprod\nda205874\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hyperphosphatemia\5351-stud-rep-contr\krx0502-305\krx0502-305-body.pdf	
<b>Primary Objectives:</b> To determine the dose-response relationship and the efficacy of fixed doses of 1, 6, and 8 g/day of ferric citrate as a dietary phosphate-binding agent in patients with ESRD on hemodialysis.	
<b>Study Design</b> This study was conducted under a special protocol assessment (SPA) agreement with the US Food and Drug Administration (FDA). This was a Phase 3, multicenter, randomized, open-label, dose-ranging and efficacy study in patients with ESRD on thrice-weekly hemodialysis. The following laboratory values were required at Screening: serum phosphorus levels $\geq 3.5$ mg/dL and $\leq 8.0$ mg/dL, serum ferritin $< 1000$ $\mu\text{g/L}$ , and TSAT $< 50\%$ . Eligible patients underwent an approximately 2-week washout from all phosphate-binding agents before starting ferric citrate treatment. Patients who had a serum phosphorus concentration $\geq 6$ mg/dL by the end of the Washout Period were eligible to be randomized in a 1:1:1 ratio to 1 of 3 fixed doses of ferric citrate (1, 6, or 8 g/day). Patients took ferric citrate as oral (b) (4) every day for 4 weeks and completed a Final Visit on Day 28. The primary efficacy outcome of this study was the change in serum phosphorus levels from baseline to end of treatment (Day 28) to show a positive dose response.	
Patients randomized to the 1 g/day dose group were instructed to take their (b) (4) at or within 1 hour of their biggest meal of the day. Patients in the 6 g/day and 8 g/day dose groups were permitted to take the total daily number of (b) (4) in any distribution with meals.	
Patients were required to maintain a diet of foods rich in vitamin D and were to remain on a constant dose of vitamin D (or its analogs) throughout the study. Calcium supplements were permitted at the discretion of the investigators or treating physicians, but were not to be taken with food. Patients were advised to take calcium supplements at bedtime or 2 hours or more prior to or after eating. Intravenous (IV) iron therapy was permitted for patients with serum ferritin $\leq 1000$ $\mu\text{g/L}$ and TSAT $\leq 50\%$ . The dose of IV iron was at the discretion of the investigator.	
The following drugs were not permitted during the study:	
<ul style="list-style-type: none"><li>• Oral iron therapy</li><li>• Calcium-containing drugs taken within 2 hours of food ingestion (calcium-containing drugs were permitted 2 hours or more prior to or following food ingestion or at bedtime for the purpose of raising serum calcium)</li><li>• Vitamin C supplements (patients were permitted to take daily water-soluble vitamins that included a small amount of vitamin C [e.g., Nephrocaps®, Renaphro®], but were instructed to</li></ul>	

take them 2 hours or more prior to or following food ingestion or at bedtime.)

- Any other phosphate-binding agent after the completion of Visit 1 of the Washout Period

*Reviewer's note: Vitamin D supplements were administered intravenously. Therefore, information on interaction with Vitamin D by oral route is not available from this study.*

### Study medication

KRX-0502 (Ferric citrate) ; doses of 1, 6, or 8 g/day; oral (b) (4) (1 g (b) (4) with food or within 1 hour after eating; Five batches: 555002, 555003, 555004, 555006, 555007

### Sampling schedules:

**Serum phosphate and serum calcium:** Screening, Days -7, -2, 0, 7, 14, 21 and 28

**Iron parameters** (ferritin, TSAT, serum iron, and total iron binding capacity (TIBC): Screening, Days 0, 7 and 28

**Intact parathyroid hormone (iPTH):** Days 0, 7 and 28

**Bicarbonate concentrations:** Days 0, 7 and 28

### Data Analysis Methods

The primary efficacy variable was the change in serum phosphorus from baseline to the end of the treatment period. To assess dose response, the primary efficacy variable was analyzed via a regression model with dose effect. Positive dose response would be confirmed if the null hypothesis of slope=0 was rejected at a significance level of 0.05. Each of the 3 dose groups (1, 6, and 8 g/day) was included in the regression analysis.

The change in serum phosphorus from baseline to endpoint was analyzed as a secondary outcome using an analysis of covariance (ANCOVA) model with treatment as the fixed class effect and baseline as the covariate. The 3 pairwise comparisons were tested in the following order at a 5% significance level: 8 g versus 1 g ; 6 g versus 1 g ; 8 g versus 6 g

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

### Study population

No. of Groups	3	<input checked="" type="checkbox"/> 1 g/day	<input checked="" type="checkbox"/> 6 g/day	<input checked="" type="checkbox"/> 8 g/day
No. of Subject		50	51	45
Age, Mean(range)		55.9(31-83)	56.5(28-89)	52.8(28-78)
Body Weight, kg		93.3	92.4	94.4
Mean(range)		(42.0-152.8)	(43.4-174.8)	(43.0-182.3)

### Results:

#### Dose-Response

- In the primary analysis, the dose-response relationship for the change in serum phosphorus from baseline was analyzed using an ANCOVA regression model that showed a statistically significant slope ( $P < 0.0001$ ).

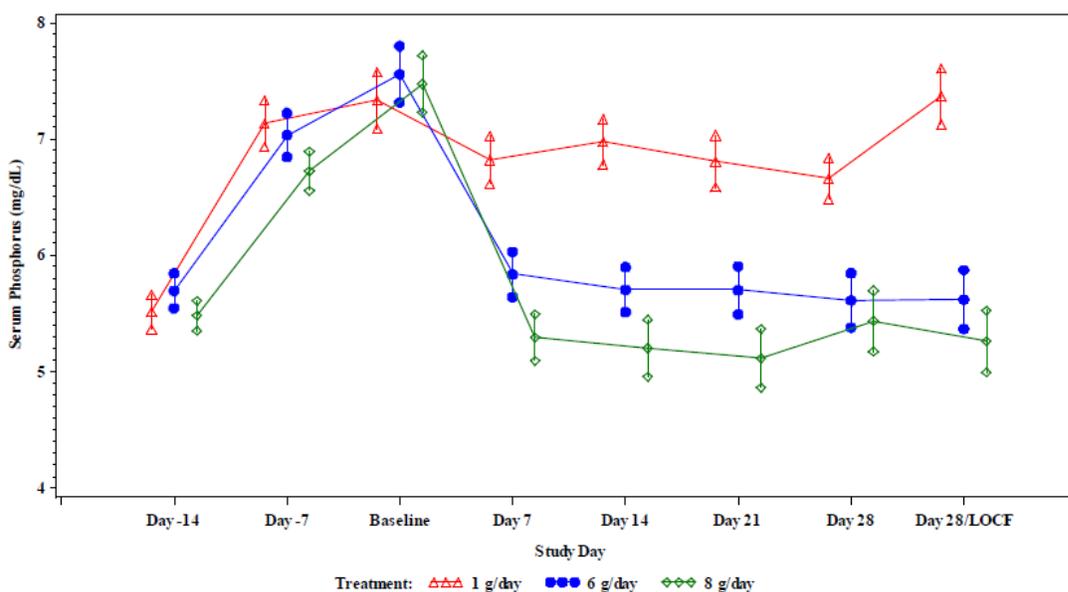
Model Variable	Degree of Freedom	Estimate (SE)	P-Value
Intercept ( $\beta$ )	1	0.3096 (0.2843)	0.2779
Coefficient for Dose ( $\beta_1$ )	1	-0.3376 (0.0498)	<0.0001

Source: Table 12.1.1

Note: Simple Regression Model: Change from Baseline at Day 28/LOCF= $\beta_0+\beta_1*\text{dose}$ .

### Serum Phosphorus levels

- Mean serum phosphorus levels peaked at baseline (Study Drug Initiation Visit), after completion of the Washout Period and were similar in the 1, 6, and 8 g/day groups at the initiation of treatment.
- Following treatment, mean serum phosphorous levels declined rapidly in the 6 g/day and 8 g/day groups and had returned to near Screening levels by Day 7.
- In the 1 g/day group, mean phosphorous levels declined only slightly by Day 7 and remained well above Screening levels throughout the Treatment Period.
- In all groups, mean values remained relatively stable between Day 7 and the remainder of the 28-day Treatment Period.
- In the ANCOVA analysis, the mean differences in the change from baseline values between the 1 g/day group and the 6 g/day and 8 g/day groups were statistically significant ( $p<0.0001$ ), while the difference between the 6 g/day and 8 g/day groups was not ( $p=0.4864$ ).



Source: Figure 12.1.1

**Table 8: Mean Observed Change from Baseline at Day 28 and Pairwise Comparisons**

Visit	1 g/day (N=50)	6 g/day (N=51)	8 g/day (N=45)
Day 28/Observed Change from Baseline			
n	38	44	34
Mean (SD)	-0.10 (1.285)	-1.86 (1.692)	-2.13 (1.998)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		1.28	1.49
95% CI		(0.69, 1.87)	(0.86, 2.12)
P-Value		<0.0001	<0.0001
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			0.21
95% CI			(-0.39, 0.81)
P-Value			0.4864

<sup>a</sup> Ferric citrate (1, 6, and 8 grams) pairwise compared with each other, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

Source: [Table 12.1.2.1](#)

### Serum Calcium Levels

- At the end of treatment, the mean serum calcium levels were unchanged from baseline in the 1 g/day group and had increased by approximately 0.2 and 0.3 mg/dL compared with baseline in the 6 g/day and 8 g/day groups, respectively. In the ANCOVA analysis, the mean observed difference in the change from baseline between the 1 g/day and 8 g/day groups was statistically significant (p=0.0077), but the mean observed difference between the 1 g/day and 6 g/day groups was not (p=0.0917).
- In the analysis of LOCF data, mean serum calcium levels increased at Day 28 compared with baseline for all 3 groups; however, no significant differences were noted between the groups.
- While the observed changes in serum calcium suggested a numerical trend for dose response, results of the regression analysis were not statistically significant (p=0.0702).

**Table 13: Summary of Serum Calcium (mg/dL) Showing Change from Baseline to Day 28/Observed and Day 28/LOCF, ITT Population**

Visit	1 g/day (N=50)	6 g/day (N=51)	8 g/day (N=45)
Baseline			
n	50	51	45
Mean (SD)	8.99 (0.774)	8.92 (0.923)	8.86 (0.800)
Day 28/Observed Change from Baseline			
n	38	44	34
Mean (SD)	-0.01 (0.379)	0.22 (0.519)	0.35 (0.622)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		-0.18	-0.30
95% CI		(-0.38, 0.03)	(-0.52, -0.08)
P-Value		0.0917	0.0077
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			-0.12
95% CI			(-0.33, 0.09)
P-Value			0.2475
Day 28/LOCF Change from Baseline			
n	50	51	45
Mean (SD)	0.04 (0.606)	0.18 (0.592)	0.27 (0.590)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		-0.11	-0.18
95% CI		(-0.31, 0.09)	(-0.39, 0.03)
P-Value		0.2925	0.0975
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			-0.07
95% CI			(-0.28, 0.14)
P-Value			0.5166

<sup>a</sup> Ferric citrate (1, 6, and 8 grams) pairwise compared with each other, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

Sources: [Table 12.2.2.1](#) and [Table 12.2.2.2](#)

**Table 14: Dose-Response Regression Analysis of Change from Baseline in Serum Calcium (mg/dL) at Day 28/LOCF, ITT Population**

Model Variable	Degree of Freedom	Estimate (SE)	P-Value
Intercept ( $\beta$ )	1	0.0087 (0.0959)	0.9278
Coefficient for Dose ( $\beta_1$ )	1	0.0306 (0.0168)	0.0702

Note: Simple Regression Model: Change from Baseline at Day 28/LOCF= $\beta_0+\beta_1$ \*dose.

Source: [Table 12.2.1](#)

### Serum Calcium x Phosphorus Levels

- Mean serum calcium × phosphorus (Ca x P) product was lower than baseline in all 3 treatment groups at each timepoint, with the largest decreases observed in the 6 g/day and 8 g/day groups. In the ANCOVA analyses, the mean observed differences in the change from baseline between the 1 g/day group and the 6 g/day and 8 g/day groups were statistically significant (p<0.0001), but the mean observed difference between the 6 g/day and 8 g/day groups was not.
- The dose response was confirmed by regression analysis (p<0.0001).

**Table 15: Summary of Serum Calcium Times Phosphorus Product (mg<sup>2</sup>/dL<sup>2</sup>) Showing Change from Baseline to Day 28/Observed and Day 28/LOCF, ITT Population**

Visit	1 g/day (N=50)	6 g/day (N=51)	8 g/day (N=45)
Baseline			
n	50	51	45
Mean (SD)	65.6 (15.79)	67.1 (15.48)	66.1 (14.92)
Day 28/Observed Change from Baseline			
n	38	44	34
Mean (SD)	-0.7 (11.57)	-15.0 (15.35)	-17.2 (16.88)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		11.39	13.16
95% CI		(5.93, 16.84)	(7.33, 18.99)
P-Value		0.0001	<0.0001
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			1.78
95% CI			(-3.79, 7.34)
P-Value			0.5287
Day 28/LOCF Change from Baseline			
n	50	51	45
Mean (SD)	1.0 (13.16)	-16.0 (16.87)	-18.6 (18.18)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		16.32	19.42
95% CI		(10.63, 22.02)	(13.55, 25.29)
P-Value		<0.0001	<0.0001
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			3.10
95% CI			(-2.75, 8.94)
P-Value			0.2971

<sup>a</sup> Ferric citrate (1, 6, and 8 grams) pairwise compared with each other, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

Sources: [Table 12.3.2.1](#) and [Table 12.3.2.2](#)

**Table 16: Dose-Response Regression Analysis of Change from Baseline in Serum Calcium Times Phosphorus Product ( $\text{mg}^2/\text{dL}^2$ ) at Day 28/LOCF, ITT Population**

Model Variable	Degree of Freedom	Estimate (SE)	P-Value
Intercept ( $\beta$ )	1	3.4569 (2.6037)	0.1864
Coefficient for Dose ( $\beta_1$ )	1	-2.9423 (0.4557)	<0.0001

Note: Simple Regression Model: Change from Baseline at Day 28/LOCF= $\beta_0+\beta_1*\text{dose}$ .

Source: [Table 12.3.1](#)

### Iron Parameters (Ferritin, Transferrin Saturation (TSAT))

#### Ferritin

- At the end of treatment, mean ferritin values decreased slightly in the 1 g group and increased in the 6 and 8 g groups. The differences between the 1 g/day group and the 6 g/day and 8 g/day groups were statistically significant, but the mean observed difference between the 6 g/day and 8 g/day groups was not.
- The dose response was confirmed by regression analysis ( $p=0.0194$ ).

**Table 17: Summary of Ferritin (mg/dL) Showing Change from Baseline to Day 28/Observed and Day 28/LOCF, ITT Population**

Visit	1 g/day (N=50)	6 g/day (N=51)	8 g/day (N=45)
Baseline			
n	50	51	45
Mean (SD)	558.2 (290.34)	515.2 (267.46)	527.0 (243.41)
Day 28/Observed Change from Baseline			
n	38	44	34
Mean (SD)	-14.4 (155.01)	90.1 (198.57)	90.2 (278.97)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		-94.72	-104.28
95% CI		(-185.47, -3.97)	(-200.78, -7.78)
P-Value		0.0409	0.0344
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			-9.56
95% CI			(-103.10, 83.99)
P-Value			0.8400
Day 28/LOCF Change from Baseline			
n	39	44	34
Mean (SD)	-12.7 (153.35)	90.1 (198.57)	90.2 (278.97)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		-92.92	-102.47
95% CI		(-182.68, -3.15)	(-197.99, -6.94)
P-Value		0.0426	0.0357
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			-9.55
95% CI			(-102.72, 83.61)
P-Value			0.8394

<sup>a</sup> Ferric citrate (1, 6, and 8 grams) pairwise compared with each other, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and p-value for testing mean difference equal to zero.

Sources: [Table 12.4.2.1](#) and [Table 12.4.2.2](#)

**Table 18: Dose-Response Regression Analysis of Change from Baseline in Ferritin (mg/dL) at Day 28/LOCF, ITT Population**

Model Variable	Degree of Freedom	Estimate (SE)	P-value
Intercept ( $\beta$ )	1	-23.4172 (38.7631)	0.5470
Coefficient for Dose ( $\beta_1$ )	1	16.1318 (6.8026)	0.0194

Note: Simple Regression Model: Change from Baseline at Day 28/LOCF= $\beta_0+\beta_1*\text{dose}$ .

Source: [Table 12.4.1](#)

### Transferrin Saturation (TSAT)

- At the end of treatment, the mean observed TSAT values decreased slightly in the 1 g/day group and increased slightly in the 6 g/day and 8 g/day groups. Although the data suggested a dose response, the data were highly variable, and no significant differences were noted among the dose groups.
- A positive dose response was not confirmed by regression analysis.

**Table 19: Summary of TSAT (%) Showing Change from Baseline to Day 28/Observed and Day 28/LOCF, ITT Population**

Visit	1 g/day (N=50)	6 g/day (N=51)	8 g/day (N=45)
Baseline			
n	50	51	45
Mean (SD)	31.9 (11.27)	33.8 (13.56)	29.8 (9.72)
Day 28/Observed Change from Baseline			
n	38	44	34
Mean (SD)	-0.8 (10.65)	1.5 (17.01)	4.4 (12.86)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		-3.85	-3.78
95% CI		(-8.94, 1.23)	(-9.20, 1.63)
P-Value		0.1362	0.1691
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			0.07
95% CI			(-5.22, 5.36)
P-Value			0.9794
Day 28/LOCF Change from Baseline			
n	39	44	34
Mean (SD)	-0.6 (10.57)	1.5 (17.01)	4.4 (12.86)
Comparison with 1 g/day <sup>a</sup>			
Mean Difference		-3.78	-3.71
95% CI		(-8.81, 1.25)	(-9.07, 1.65)
P-Value		0.1392	0.1731
Comparison with 6 g/day <sup>a</sup>			
Mean Difference			0.07
95% CI			(-5.19, 5.34)
P-Value			0.9780

<sup>a</sup> Ferric citrate (1, 6, and 8 grams) pairwise compared with each other, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and p-value for testing mean difference equal to zero.

Sources: [Table 12.5.2.1](#) and [Table 12.5.2.2](#)

**Table 20: Dose-Response Regression Analysis of Change from Baseline in TSAT (%) at Day 28/LOCF, ITT Population**

Model Variable	Degree of Freedom	Estimate (SE)	P-Value
Intercept (β)	1	-1.5264 (2.5373)	0.5486
Coefficient for Dose (β1)	1	0.6480 (0.4453)	0.1483

Simple Regression Model: Change from Baseline at Day 28/LOCF=β0+β1\*dose.

Source: [Table 12.5.1](#)

### Serum Bicarbonate Levels

- At the end of treatment, the mean observed bicarbonate values increased slightly in all 3 groups, with larger increases in the 6 g/day and 8 g/day groups. The differences between treatment groups were not significant.
- A positive dose response was confirmed by regression analysis ( $p=0.0261$ ).

**Table 21: Summary of Bicarbonate (mEq/L) Showing Change from Baseline to Day 28/Observed and Day 28/LOCF, ITT Population**

Visit	1 g/day (N=50)	6 g/day (N=51)	8 g/day (N=45)
<b>Baseline</b>			
n	49	51	44
Mean (SD)	23.0 (2.70)	22.5 (3.15)	22.6 (3.34)
<b>Day 28/LOCF</b>			
n	38	44	34
Mean (SD)	23.3 (2.72)	24.0 (3.30)	24.1 (3.32)
<b>Day 28/Observed Change from Baseline</b>			
n	37	44	33
Mean (SD)	0.1 (2.37)	1.6 (3.05)	1.5 (3.92)
<b>Comparison with 1 g/day<sup>a</sup></b>			
Mean Difference		-1.11	-1.09
95% CI		(-2.32, 0.11)	(-2.39, 0.22)
P-Value		0.0738	0.1009
<b>Comparison with 6 g/day<sup>a</sup></b>			
Mean Difference			0.02
95% CI			(-1.23, 1.27)
P-Value			0.9758
<b>Day 28/LOCF Change from Baseline</b>			
n	38	44	33
Mean (SD)	0.1 (2.35)	1.6 (3.05)	1.5 (3.92)
<b>Comparison with 1 g/day<sup>a</sup></b>			
Mean Difference		-1.10	-1.08
95% CI		(-2.30, 0.10)	(-2.37, 0.21)
P-Value		0.0726	0.0998
<b>Comparison with 6 g/day<sup>a</sup></b>			
Mean Difference			0.02
95% CI			(-1.22, 1.26)
P-Value			0.9757

<sup>a</sup> Ferric citrate (1, 6, and 8 grams) pairwise compared with each other, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and p-value for testing mean difference equal to zero.

Source: [Table 12.6.2.1](#) and [Table 12.6.2.2](#)

**Table 22: Dose-Response Regression Analysis of Change from Baseline in Bicarbonate (mEq/L) at Day 28/LOCF, ITT Population**

Model Variable	Degree of Freedom	Estimate (SE)	P-Value
Intercept ( $\beta$ )	1	-0.0382 (0.5777)	0.9474
Coefficient for Dose ( $\beta_1$ )	1	0.2286 (0.1014)	0.0261

Simple Regression Model: Change from Baseline at Day 28/LOCF= $\beta_0+\beta_1$ \*dose.

Source: Table 12.6.1

### Exploratory Assessments- 25-Hydroxyvitamin D Levels

- Vitamin D levels were variable between patients, but mean values remained fairly stable throughout the study in all groups.
- No temporal or dose-related trends were apparent.

**Table 23: Summary of 25-Hydroxyvitamin D Levels (ng/mL)**

Visit	1 g/day	6 g/day	8 g/day
Baseline			
n	14	18	14
Mean (SD)	22.58 (16.655)	23.46 (10.837)	20.70 (10.475)
Day 7 Change from Baseline			
n	14	18	11
Mean (SD)	-0.13 (5.529)	-1.82 (3.761)	0.78 (3.088)
Day 14 Change from Baseline			
n	13	17	14
Mean (SD)	1.45 (5.326)	-2.63 (6.907)	2.36 (2.966)
Day 21 Change from Baseline			
n	12	16	14
Mean (SD)	-0.31 (5.143)	-2.45 (7.771)	-0.34 (4.215)
Day 28 Change from Baseline			
n	14	17	13
Mean (SD)	1.07 (5.803)	-1.17 (4.667)	-0.53 (2.889)

Source: Table 14.6

### Safety

#### Death: None

- The overall incidence of AEs was lowest in the 1 g/day group (66.7%) and was similar in the 6 g/day group (82.7%) and in the 8 g/day group (85.4%).
- Across all dose groups, most AEs were mild or moderate in severity. The incidence of severe AEs was low and similar in the 1 g/day (13.7%) and 6 g/day (9.6%) groups and was considerably higher in the 8 g/day group (31.3%).
- The incidence of drug-related AEs, SAEs, and AEs leading to study drug discontinuation increased with increasing dose.

**Table 25: Overall Summary of Adverse Events**

Category	1 g/day (N=51)	6 g/day (N=52)	8 g/day (N=48)	Total (N=151)
	<b>n (%)</b>			
Patients with an AE <sup>a</sup>	34 (66.7)	43 (82.7)	41 (85.4)	118 (78.1)
Maximum intensity of AEs				
Mild	18 (35.3)	20 (38.5)	17 (35.4)	55 (36.4)
Moderate	9 (17.6)	18 (34.6)	9 (18.8)	36 (23.8)
Severe	7 (13.7)	5 (9.6)	15 (31.3)	27 (17.9)
Patients with a drug-related AE <sup>b</sup>	15 (29.4)	18 (34.6)	20 (41.7)	53 (35.1)
Patients with an SAE	6 (11.8)	7 (13.5)	9 (18.8)	22 (14.6)
Patients with a drug-related SAE	0	1 (1.9)	0	1 (0.7)
Patients who withdrew due to an AE	2 (3.9)	3 (5.8)	8 (16.7)	13 (8.6)
Patients who died	0	0	0	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

<sup>a</sup> AEs that occurred between Day 0 and 30 days post-treatment are included. A patient who experienced the same AE more than once was counted only once in the incidence for that event and at the highest severity for that event.

<sup>b</sup> Related AEs were defined as AEs with a “Suspect” relationship to study drug.

Sources: [Table 14.2](#), [Table 14.3](#), and [Table 14.4](#), and [Appendix 16.2, Listing 7](#)

## Conclusion

- The dose-response relationship was confirmed by regression analysis. Administration of 1, 6, and 8 g/day of ferric citrate produced dose-dependent decreases in mean serum phosphorus concentrations by Day 7 after treatment. Mean serum phosphorous concentrations remained relatively stable throughout the remainder of the Treatment Period. At the Final Visit, mean decreases in serum phosphorous in the 1 g/day, 6 g/day and 8 g/day groups were -0.10, -1.86, and -2.13 mg/dL, respectively.
- Slight increases in serum calcium levels (0.2 to 0.3 mg/dL) were observed in the 6 g/day and 8 g/day groups at Day 28.
- There was a dose-dependent decrease from baseline in the calcium×phosphorus product.
- There was a small dose-dependent increase from baseline in ferritin. The increases in the 6 g/day and 8 g/day groups were statistically significant compared with the 1 g/day group.
- TSAT values decreased slightly at Day 28 in the 1 g/day group and increased slightly in the 6 g/day and 8 g/day groups. Results of the ANCOVA and regression analyses were not significant.
- There was a trend toward dose-dependent increases from baseline in bicarbonate values, but the increases in the 6 g/day and 8 g/day groups were not significantly different from the 1 g/day group.
- Ferric citrate at doses of 1 and 6 g/day was generally safe and well tolerated in this study.

## Dose Ranging Study

<b>Study Report #</b> PBB00101	<b>Study period</b> 04/30/04-08/31/05
<p><b>Title:</b> A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Effects of Ferric Citrate on Serum Phosphate in Patients with End Stage Renal Disease (ESRD)</p> <p><b>EDR Link:</b> \\cdsesub1\evsprod\nda205874\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hyperphosphatemia\5351-stud-rep-contr\pbb00101\pbb00101-body.pdf</p>	
<p><b>Primary Objectives</b></p> <p>To determine the effect and evaluate the safety of ferric citrate at doses of 2, 4, and 6 grams daily, administered three times a day (TID) for 28 days on serum phosphorus levels in patients with ESRD.</p> <p><b>Study Design:</b> This was a randomized, double-blind, placebo-controlled, dose-ranging study to assess the effect of ferric citrate on serum phosphorus concentrations in patients with ESRD who were undergoing hemodialysis. Patients who met the inclusion/exclusion criteria at Visit 1 underwent a one- to two-week washout from all phosphate-binding agents. Patients who had a serum phosphorus <math>\geq 5.5</math> mg/dL and <math>\leq 10</math> mg/dL by the end of this washout period (at Visit 2 or by Visit 3) were eligible to be randomized to one of four treatment groups in a ratio of 2:2:2:1 (ferric citrate 2, 4, and 6 g/day and placebo, respectively). The primary efficacy variable was the change from baseline to Day 14 and Day 28 in phosphorus concentration. The secondary efficacy variable was the change from baseline to Day 14 and Day 28 in the Ca times Phosphorus product (Ca x P). Other variables included change from baseline to Day 14 and Day 28 in Ca, serum iron and ferritin concentration and transferrin saturation percentage and total iron binding capacity (IBC).</p> <p>At Visit 3 (Day 0), all patients received randomized study drug (4 capsules TID) and were instructed to begin taking capsules within 10 minutes of completing their next meal.</p> <p>Patients who had been receiving a stable dose of vitamin D or calcitriol for 1 month prior to study enrollment were instructed to maintain their current dose throughout the study. Patients who were not taking vitamin D or calcitriol prior to enrollment could not be started on these medications during the study period. No medications or over-the-counter (OTC) preparations containing aluminum, Ca, phosphates or magnesium, or that could interfere with phosphate or Ca absorption were allowed from the start of the washout period until the end of the study. No iron-containing medications could be taken during the study.</p>	
<p><b>Study medication</b></p> <p>Ferric Citrate Capsules 500 mg in 3 daily doses totaling up to 2g, 4g or 6g; Lot number: 9621          Placebo Capsules in 3 daily doses; Lot number: 9562</p>	
<p><b>Sampling schedules:</b></p> <p><b>Serum phosphate and serum calcium:</b> Screening, Days -7, 0, 14 and 28  <b>Iron parameters</b> (serum iron, total IBC, ferritin, and transferrin saturation percentage): Screening, Days 0, 14 and 28</p>	
<p><b>Data Analysis Methods</b></p> <p>Descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) were used to summarize phosphorus concentrations by treatment group at screening, Day -7, Day 0, Day 14, and Day 28.</p>	

The primary efficacy variable was change in phosphorus concentration from baseline (Day 0) to Day 14 and

Day 28. These changes were descriptively summarized by treatment group. The mean changes were plotted against time (Day 14 and Day 28) by treatment group.

The 3 ferric citrate treatment groups were compared to the placebo treatment group using a one-way analysis of variance model with a fixed effect for treatment group.

For patients in the treatment group, Day 14 and Day 28 changes in phosphorus concentration were separately analyzed as the dependent variable in a linear regression on the dose levels (2 g, 4 g, 6 g). Model significance from the linear regression was reported using the F-test P-value. The model predicted change for each dose level was reported.

### Study population

No. of Groups	4	<input checked="" type="checkbox"/> Placebo	<input checked="" type="checkbox"/> 2 g/day	<input checked="" type="checkbox"/> 4 g/day	<input checked="" type="checkbox"/> 6 g/day
No. of Subject		16	31	32	32
Age, Mean(range)		49.6(19-62)	48.8(22-81)	54.6(28-83)	47.3(19-70)
Body Weight, kg Mean(range)		74.3 (47.3-126.7)	73.4 (46.8-127.9)	76.2 (45.6-139.0)	80.1 (40.3-147.0)
Race, N(%)					
Caucasian		1(12.5)	2(6.5)	0(0.0)	0(0.0)
African-American		6(37.5)	12(38.7)	16(50.0)	12(37.5)
Hispanic/Latino		1(6.3)	1(3.2)	3(9.4)	4(12.5)
Asian/Pacific Islander		7(43.8)	16(51.6)	13(40.6)	15(45.9)
Other		0(0.0)	0(0.0)	0(0.0)	1(3.1)

### Results:

#### Serum Phosphorus levels

- On Day 14, there was a small but apparent dose-related decrease in the treatment groups compared with Day 0, in the mean serum phosphorus concentration (-0.3, -0.8, and -1.2 mg/dL decrease in the 2, 4, and 6 g/day ferric citrate groups, respectively) but the mean difference from placebo was not statistically significant.
- On Day 28, there continued to be an apparent dose-related decrease in the treatment groups, when compared with Day 0, in the mean serum phosphorus concentration (-0.3, -1.1, and -1.5 mg/dL decrease in the 2, 4, and 6 g/day ferric citrate groups, respectively). The placebo comparison mean difference (-1.5 mg/dL) was statistically significant (P=0.0119) only in the 6 g/day ferric citrate group while in the 4 g/day group mean difference did not approach statistical significance (-1.1 mg/dL mean difference from placebo; P=0.0610).

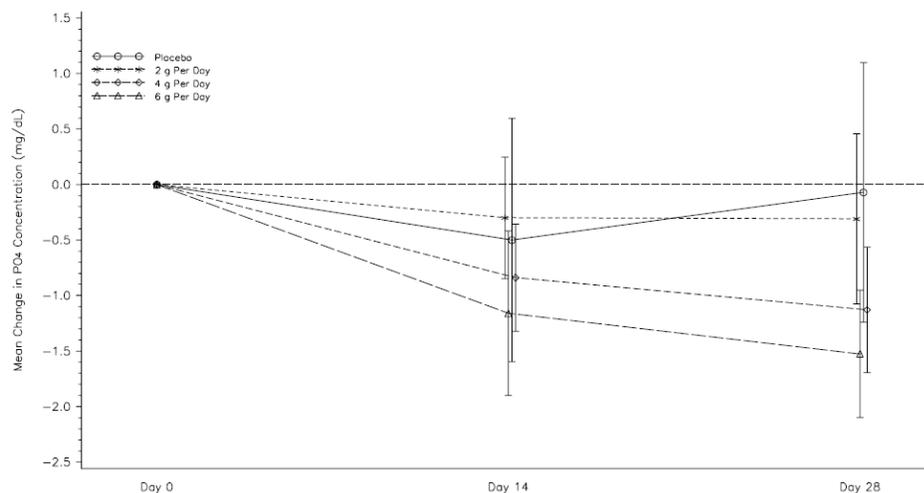
**Table 11-1: Summary Analysis of Serum PO<sub>4</sub> Concentration (mg/dL) at Screening, Day -7, and Day 0 Showing Change from Day 0 to Day 14 and Day 28**

Day		Placebo	2 g/day	4 g/day	6 g/day
		Observed	Observed	Observed	Observed
-30/-15	N	16	31	32	32
	Mean	5.4	5.8	6.3	5.7
	SD	1.46	1.85	1.44	1.09
	Median	5.4	5.6	5.8	5.5
	Min, Max	2.6, 8.5	1.9, 10.0	4.0, 9.6	3.6, 8.4
-7	N	13	25	25	25
	Mean	6.7	6.6	7.1	6.9
	SD	2.14	1.82	1.25	1.54
	Median	6.3	6.7	6.9	6.8
	Min, Max	2.6, 10.5	3.2, 10.0	4.0, 9.9	4.5, 10.6
0	N	16	31	32	32
	Mean	7.2	7.2	7.1	7.3
	SD	1.43	1.23	1.27	1.33
	Median	6.7	7.0	6.9	7.2
	Min, Max	5.8, 10.5	5.2, 10.3	4.5, 9.9	5.5, 10.6
14		<b>Change from Day 0</b>			
	N	15	21	29	27
	Mean	-0.5	-0.3	-0.8	-1.2
	SD	1.98	1.20	1.27	1.87
	Median	0.4	-0.3	-0.9	-1.3
	Min, Max	-5.8, 1.6	-4.0, 1.6	-2.9, 2.8	-4.5, 2.3
Placebo Comparison <sup>a</sup>					
Mean Difference			0.2	-0.3	-0.7
95% CI			(-0.9, 1.3)	(-1.3, 0.7)	(-1.9, 0.6)
P-Value			0.7086	0.4948	0.2899
28 <sup>b</sup>		<b>Change from Day 0</b>			
	N	14	31	32	32
	Mean	-0.1	-0.3	-1.1	-1.5
	SD	2.02	2.09	1.57	1.59
	Median	0.1	-0.5	-1.0	-1.5
	Min, Max	-4.2, 2.3	-3.6, 6.7	-5.3, 1.8	-4.8, 2.6
Placebo Comparison <sup>a</sup>					
Mean Difference			-0.2	-1.1	-1.5
95% CI			(-1.6, 1.1)	(-2.2, 0.1)	(-2.6, -0.3)
P-Value			0.7224	0.0610	0.0119

Cross Reference: Table 14.2.1.

- (a) Ferric citrate (2, 4, and 6 grams) separately compared with placebo, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.
- (b) Day 28 includes Early Termination Visit.

Figure 14.4.1  
PO<sub>4</sub> Concentration Mean Change from Day 0 by Study Day and Treatment Group  
Population: Efficacy



## Dose-Response

- For patients in the treatment group, Day 14 and Day 28 changes in phosphorus concentration were separately analyzed as the dependent variable in a linear regression on the dose level of ferric citrate. For Study Day 14, dose level did not quite reach statistical significance as a predictor of change in phosphorus concentration (P=0.0523). For Study Day 28, dose level was a clearly statistically significant predictor of change in phosphorus concentration (P=0.0073).

Table 14.2.6  
Summary of Linear Regression of Efficacy Variable on Ferric Citrate Dose for All Efficacy Variables  
Population: Efficacy

Day	Efficacy Variable	Units	Model P-value	Predicted Change		
				2 g Per Day	4 g Per Day	6 g Per Day
14	Change in PO4 Concentration	mg/dL	0.0523	-0.35	-0.77	-1.20
	Change in Ca Concentration	mg/dL	0.4274	0.41	0.34	0.27
	Change in Ca x PO4	(mg/dL) <sup>2</sup>	0.0401	-0.25	-4.67	-9.08
	Change in Serum Iron Concentration	ug/mL	0.6023	3.52	5.93	8.33
	Change in Ferritin Concentration	ng/mL	0.2408	66.61	43.89	21.17
	Change in Transferrin Saturation Percentage	%	0.5559	0.86	1.93	3.00
	Change in Total IBC	-	0.8022	4.49	5.62	6.75
28	Change in PO4 Concentration	mg/dL	0.0073	-0.38	-0.99	-1.59
	Change in Ca Concentration	mg/dL	0.7354	0.23	0.26	0.28
	Change in Ca x PO4	(mg/dL) <sup>2</sup>	0.0158	-1.73	-7.00	-12.27
	Change in Serum Iron Concentration	ug/mL	0.6470	1.35	2.88	4.40
	Change in Ferritin Concentration	ng/mL	0.4819	2.16	17.12	32.07
	Change in Transferrin Saturation Percentage	%	0.6714	0.26	0.91	1.56
	Change in Total IBC	-	0.9020	3.73	3.18	2.63

## Serum Calcium Levels

- On Day 14 and 28 there were slight increases (range of 0.03 to 0.42 mg/dL) in mean serum Ca concentration in all treatment groups compared with Study Day 0. However, there was no statistically significant change when compared with placebo in serum Ca concentration from Day 0 to either Day 14 or Day 28.

**Table 11-2: Summary Analysis of Serum Calcium Concentration (mg/dL) at Screening and on Day 0 and Change from Day 0 to Day 14 and Day 28**

Day		Placebo	2 g/day	4 g/day	6 g/day
		Observed	Observed	Observed	Observed
-30/-15	N	16	31	32	32
	Mean	9.18	9.39	9.33	9.25
	SD	0.556	0.846	0.937	0.795
	Median	9.2	9.6	9.6	9.2
	Min, Max	8.2, 10.1	7.5, 10.5	6.6, 10.9	6.5, 10.7
0	N	16	31	32	32
	Mean	8.71	8.78	9.02	8.99
	SD	0.779	0.981	0.913	0.812
	Median	8.8	8.9	9.1	9.1
	Min, Max	7.2, 10.0	6.7, 10.3	7.0, 10.4	6.3, 10.5
		Change from Day 0			
14	N	15	21	29	27
	Mean	0.28	0.35	0.42	0.23
	SD	0.711	0.753	0.528	0.478
	Median	0.1	0.2	0.5	0.3
	Min, Max	-0.9, 1.7	-1.1, 2.0	-0.6, 1.7	-0.8, 1.0
Placebo Comparison <sup>a</sup>					
Mean Difference			0.1	0.1	-0.1
95% CI			(-0.4, 0.6)	(-0.2, 0.5)	(-0.4, 0.3)
P-Value			0.7874	0.4506	0.7702
		Change from Day 0			
28 <sup>b</sup>	N	15	31	32	32
	Mean	0.03	0.22	0.28	0.27
	SD	0.390	0.643	0.517	0.564
	Median	0.1	0.2	0.3	0.2
	Min, Max	-0.6, 0.7	-0.8, 2.0	-1.2, 1.3	-0.8, 1.5
Placebo Comparison <sup>a</sup>					
Mean Difference			0.2	0.3	0.2
95% CI			(-0.2, 0.6)	(-0.1, 0.6)	(-0.1, 0.6)
P-Value			0.2845	0.1016	0.1357

Cross Reference: [Table 14.2.2](#).

(a) Ferric citrate (2, 4, and 6 grams) separately compared with placebo, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

(b) Day 28 includes Early Termination Visit.

### Serum Calcium x Phosphorus Levels

- On Day 14, there was an apparent dose-related decrease in the treatment groups, when compared with Day 0, in the mean Ca x P product (-0.1, -4.9, and -8.9 mg<sup>2</sup>/dL<sup>2</sup> in the 2, 4, and 6 g/day ferric citrate groups, respectively) but the mean difference from placebo was not statistically significant.
- On Day 28, there continued to be an apparent dose-related decrease in the treatment groups, when compared with Day 0, in the mean Ca x P product (-1.1, -8.1, and -11.7 mg<sup>2</sup>/dL<sup>2</sup> in the 2, 4, and 6 g/day ferric citrate groups, respectively). The reductions were statistically different from placebo only in the 6 g/day group (P=0.0378).

**Table 11-3: Summary Analysis of Calcium Times PO<sub>4</sub> Product (mg/dL)<sup>2</sup> at Screen and on Day 0 and Change from Day 0 to Day 14 and Day 28**

Day		Placebo	2 g/day	4 g/day	6 g/day
		Observed	Observed	Observed	Observed
-30/-15	N	16	31	32	32
	Mean	49.5	54.4	57.8	52.4
	SD	11.85	16.49	11.26	10.40
	Median	50.3	52.3	55.7	52.2
	Min, Max	25.2, 69.7	19.8, 98.9	37.6, 80.8	34.9, 81.2
0	N	16	31	32	32
	Mean	62.8	62.9	63.5	65.8
	SD	13.91	13.25	10.69	12.19
	Median	62.3	59.4	63.2	66.2
	Min, Max	42.5, 94.1	48.2, 103.0	43.2, 83.2	47.9, 94.3
14		<b>Change from Day 0</b>			
	N	15	21	29	27
	Mean	-2.7	-0.1	-4.9	-8.9
	SD	16.17	14.75	11.76	17.22
	Median	3.7	0.6	-5.4	-12.1
	Min, Max	-38.4, 15.2	-41.5, 31.1	-27.2, 22.9	-37.8, 30.1
Placebo Comparison <sup>a</sup>					
Mean Difference			2.6	-2.2	-6.2
95% CI			(-7.9, 13.2)	(-10.8, 6.4)	(-17.2, 4.7)
P-Value			0.6150	0.6031	0.2572
28 <sup>b</sup>		<b>Change from Day 0</b>			
	N	14	31	32	32
	Mean	-0.3	-1.1	-8.1	-11.7
	SD	19.34	20.66	14.70	15.39
	Median	3.6	-2.3	-9.7	-13.5
	Min, Max	-34.9, 24.9	35.6, 67.2	-41.3, 21.9	-42.3, 35.2
Placebo Comparison <sup>a</sup>					
Mean Difference			-0.9	-7.9	-11.4
95% CI			(-14.0, 12.3)	(-18.3, 2.6)	(-22.2, -0.7)
P-Value			0.8950	0.1375	0.0378

Cross Reference: [Table 14.2.3](#).

(a) Ferric citrate (2, 4, and 6 grams) separately compared with placebo, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

(b) Day 28 includes Early Termination Visit.

## Iron Parameters (Serum iron, Ferritin, Transferrin Saturation Percentage, Total Iron Binding Capacity)

### Serum iron

- The placebo group had a notably higher mean and median serum iron concentration than any of the ferric citrate groups. There was a small increase in the mean serum iron concentration on Days 14 and 28, when compared with Day 0, in all ferric citrate groups which was not statistically significantly different from the mean difference for placebo. Nor was there a statistically

significant dose related change in serum iron concentration on Study Day 14 (P=0.6023) or Study Day 28 (P=0.6470).

**Table 11-4: Summary Analysis of Serum Iron Concentration ( $\mu\text{g/dL}$ ) at Screening and on Day 0 and Change from Day 0 to Day 14 and Day 28**

Day		Placebo	2 g/day	4 g/day	6 g/day
		Observed	Observed	Observed	Observed
-30/-15	N	16	31	32	32
	Mean	93.1	60.7	65.7	61.7
	SD	52.12	24.04	20.36	24.21
	Median	72.5	59.0	64.5	56.5
	Min, Max	53, 250	22, 136	25, 108	26, 128
0	N	16	31	31	32
	Mean	90.6	61.1	63.2	63.8
	SD	39.12	23.10	21.38	26.00
	Median	85.5	56.0	58.0	59.0
	Min, Max	46, 184	26, 119	32, 103	33, 140
14		<b>Change from Day 0</b>			
	N	15	21	28	27
	Mean	2.2	6.5	1.5	10.6
	SD	43.43	29.71	29.14	35.52
	Median	8.0	8.0	-1.5	4.0
	Min, Max	-84, 79	-49, 70	-63, 60	-70, 137
Placebo Comparison <sup>a</sup>					
Mean Difference			4.3	-0.7	8.4
95% CI			(-20.5, 29.0)	(-23.1, 21.7)	(-16.6, 33.5)
P-Value			0.7275	0.9500	0.5002
28 <sup>b</sup>		<b>Change from Day 0</b>			
	N	15	31	31	32
	Mean	-2.5	2.4	0.9	5.4
	SD	28.03	26.99	25.12	27.20
	Median	0.0	0.0	8.0	6.5
	Min, Max	-51, 45	-41, 85	-73, 44	-87, 49
Placebo Comparison <sup>a</sup>					
Mean Difference			4.9	3.4	7.9
95% CI			(-12.4, 22.2)	(-13.1, 19.9)	(-9.4, 25.2)
P-Value			0.5724	0.6801	0.3623

Cross Reference: [Table 14.2.4](#).

- (a) Ferric citrate (2, 4, and 6 grams) separately compared with placebo, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.
- (b) Day 28 includes Early Termination Visit.

## Ferritin

- There was an increase in the mean serum ferritin concentration on Day 14, when compared with Day 0, in all ferric citrate groups but this was not statistically significant when compared with the

mean difference from placebo.

- On Day 28, only the 2 and 6 g/day ferric citrate groups showed this increase relative to Day 0 in mean serum ferritin concentration, but it was also not statistically significant when compared with the mean difference from placebo (P=0.5504 for the 2 g/day and P=0.9370 for the 6 g/day); nor was there a statistically significant relationship of change in serum ferritin concentration to ferric citrate dose level on Study Day 14 (P=0.2408) or Study Day 28 (P=0.4819).

**Table 11-5: Summary Analysis of Serum Ferritin Concentration (ng/mL) at Screen and on Day 0 and Change from Day 0 to Day 14 and Day 28**

Day		Placebo	2 g/day	4 g/day	6 g/day
		Observed	Observed	Observed	Observed
-30/-15	N	16	31	32	32
	Mean	493.8	429.3	502.2	488.6
	SD	209.25	240.56	244.79	217.26
	Median	452.0	409.0	511.5	480.0
	Min, Max	157, 827	11, 888	23, 1000	79, 857
0	N	16	31	31	31
	Mean	435.9	397.7	461.1	468.5
	SD	192.07	217.85	238.40	227.51
	Median	376.5	398.0	503.0	429.0
	Min, Max	151, 849	8, 832	22, 1028	83, 1121
14		<b>Change from</b>	<b>Change from</b>	<b>Change from</b>	<b>Change from</b>
		<b>Day 0</b>	<b>Day 0</b>	<b>Day 0</b>	<b>Day 0</b>
	N	15	21	28	26
	Mean	25.6	56.9	58.5	13.3
	SD	157.76	151.98	124.16	121.48
	Median	-4.0	17.0	38.5	-21.0
	Min, Max	-167, 415	-183, 479	-163, 374	-258, 259
Placebo Comparison <sup>a</sup>					
Mean Difference			31.3	32.9	-12.3
95% CI			(-74.8, 137.3)	(-55.3, 121.1)	(-101.2, 76.7)
P-Value			0.5531	0.4558	0.7813
28 <sup>b</sup>		<b>Change from</b>	<b>Change from</b>	<b>Change from</b>	<b>Change from</b>
		<b>Day 0</b>	<b>Day 0</b>	<b>Day 0</b>	<b>Day 0</b>
	N	15	31	31	31
	Mean	36.4	12.0	-2.5	41.9
	SD	165.34	108.12	121.14	239.53
	Median	-13.0	5.8	23.0	29.0
	Min, Max	-201, 449	-262, 212	-242, 268	316, 1083
Placebo Comparison <sup>a</sup>					
Mean Difference			-24.4	-38.9	5.5
95% CI			(-106.3, 57.4)	(-125.6, 47.8)	(-133.1, 144.1)
P-Value			0.5504	0.3709	0.9370

Cross Reference: [Table 14.2.5](#).

(a) Ferric citrate (2, 4, and 6 grams) separately compared with placebo, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

(b) Day 28 includes Early Termination Visit.

## Transferrin Saturation Percentage

- For Days 14 and 28, there were small, but when compared with placebo, not statistically significant increases (except a small not statistically significant decreased percentage on Study Day 14 in the 4 g/day group) in mean transferrin saturation percentages. No statistically significant dose related change in transferrin saturation percentage was found on Study Day 14 (P=0.5559) or Study Day 28 (P=0.6714).

**Table 11-6: Summary Analysis of Serum Transferrin Saturation Percentage at Screen and on Day 0 and Change from Day 0 to Day 14 and Day 28**

Day		Placebo	2 g/day	4 g/day	6 g/day
		Observed	Observed	Observed	Observed
-30/-15	N	16	31	32	32
	Mean	38.9	27.2	31.1	28.5
	SD	15.86	8.31	9.43	10.72
	Median	34.5	27.2	29.7	27.4
	Min, Max	19.0, 70.0	11.0, 47.3	11.0, 53.0	13.0, 56.1
0	N	16	31	30	32
	Mean	36.6	27.4	29.5	30.1
	SD	14.78	8.35	9.43	14.00
	Median	33.2	27.0	29.0	27.3
	Min, Max	19, 80.8	8.2, 53.2	12.7, 56.0	10.9, 85.1
14		<b>Change from Day 0</b>			
14	N	15	21	27	27
	Mean	0.3	2.3	-0.3	4.1
	SD	17.49	13.51	11.09	12.73
	Median	4.0	3.6	-0.2	2.0
	Min, Max	-43.2, 28.0	-25.7, 26.0	-27.0, 19.7	-17.0, 33.0
Placebo Comparison <sup>a</sup>					
Mean Difference			2.1	-0.6	3.9
95% CI			(-8.4, 12.6)	(-9.5, 8.3)	(-5.6, 13.4)
P-Value			0.6912	0.8909	0.4137
28 <sup>b</sup>		<b>Change from Day 0</b>			
	N	15	31	30	32
	Mean	-1.2	0.6	0.1	1.9
	SD	11.33	11.59	12.06	12.93
	Median	3.0	-2.0	3.1	2.8
Min, Max	-32.4, 10.5	-26.1, 34.8	-31.0, 21.0	-42.6, 21.0	
Placebo Comparison <sup>a</sup>					
Mean Difference			1.8	1.3	3.1
95% CI			(-5.5, 9.1)	(-6.3, 8.8)	(-4.7, 11.0)
P-Value			0.6178	0.7345	0.4290

Cross Reference: [Table 14.2.6](#).

(a) Ferric citrate (2, 4, and 6 grams) separately compared with placebo, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

(b) Day 28 includes Early Termination Visit.

## Total Iron Binding Capacity

- On Days 14 and 28 in all ferric citrate groups there were increases in the mean total iron binding capacity but when compared with the mean differences from placebo these increases were not statistically significant. Nor was there a statistically significant dose related change found on Day 14 (P=0.8022) or Day 28 (P=0.9020).

**Table 11-7: Analysis of Change from Baseline to Day 14 and Day 28 in Total Iron Binding Capacity (µg/dL)**

Day		Placebo	2 g/day	4 g/day	6 g/day
		Observed	Observed	Observed	Observed
	N	16	31	32	32
	Mean	227.0	215.7	208.0	212.9
	SD	55.71	58.07	47.69	56.05
	Median	208.0	217.0	206.5	202.5
	Min, Max	171.0, 355.0	114.0, 362.0	118.0, 316.0	121.0, 427.0
0	N	16	31	31	32
	Mean	237.6	214.5	206.8	210.6
	SD	59.30	48.69	60.37	72.93
	Median	225.5	219.0	212.0	207.0
	Min, Max	171.0, 368.0	124.0, 333.0	28.0, 331.0	48.6, 497.0
		<b>Change from Day 0</b>			
14	N	15	21	28	27
	Mean	-0.8	1.9	9.6	4.7
	SD	37.90	22.34	36.66	30.49
	Median	1.0	2.0	9.0	2.0
	Min, Max	-110.0, 44.0	-55.0, 46.0	-80.0, 110.0	-58.0, 103.0
	Placebo Comparison <sup>a</sup>				
	Mean Difference		2.7	10.4	5.5
	95% CI		(-17.8, 23.1)	(-13.6, 34.3)	(-16.2, 27.2)
	P-Value		0.7932	0.3872	0.6103
		<b>Change from Day 0</b>			
28 <sup>b</sup>	N	15	31	31	32
	Mean	-5.3	4.8	1.1	3.6
	SD	26.32	29.06	37.18	39.73
	Median	-3.0	-1.0	0.0	2.5
	Min, Max	-69.0, 44.0	-53.0, 71.0	-61.0, 124.0	-98.0, 163.4
	Placebo Comparison <sup>a</sup>				
	Mean Difference		10.1	6.4	9.0
	95% CI		(-7.8, 28.0)	(-15.2, 28.0)	(-13.8, 31.7)
	P-Value		0.2609	0.5520	0.4312

Cross Reference: [Table 14.2.7](#).

(a) Ferric citrate (2, 4, and 6 grams) separately compared with placebo, providing mean difference of change from the Day 0 baseline, 95% confidence interval for mean difference, and P-value for testing mean difference equal to zero.

(b) Day 28 includes Early Termination Visit.

## Safety

**Death: None**

- There was no notable dose related increase in AEs in any system organ class.
- Six patients experienced a total of 14 SAEs during the study while most of them were considered not likely to be related to stud drug.

**Table 12-4: Serious Adverse Events and Relationship to Study Drug**

<b>Treatment Group</b>	<b>Patient number</b>	<b>SAE</b>	<b>Relationship</b>
4 g/day	1-01-1-002	Sleep apnea syndrome	Unlikely to be related
		Mental status change	Unlikely to be related
		Hypercapnia	Unlikely to be related
		Hypoventilation	Unlikely to be related
		Fluid overload	Unlikely to be related
		Clavicle fracture	Unlikely to be related
4 g/day	1-01-1-023	Abdominal pain	Unlikely to be related
4 g/day	1-03-1-004	Gastritis	Possibly related
		Convulsion	Unlikely to be related
6 g/day	1-02-2-004	Chest pain	Unlikely to be related
6 g/day	2-01-1-051	Pyrexia	Unlikely to be related
Placebo	1-02-1-011	Dyspnea	Unlikely to be related
		Fluid Overload	Unlikely to be related
		Pulmonary edema	Unlikely to be related

Cross Reference: Appendix 16.2, Listing 16.2.13.

**Conclusion**

- In all 3 ferric citrate groups (2, 4, and 6 g/day), there was an apparent trend for a mean decrease in serum phosphorus concentration after both 2 and 4 weeks of treatment. However only on Study Day 28 in the 6 g/day group was this mean decrease in phosphorus concentration statistically significant when compared with placebo (P=0.0119). Similar results were observed for Ca x P product.
- For Study Day 14, dose level of ferric citrate did not quite reach statistical significance as a predictor of change in phosphorus concentration (P=0.0523). For Study Day 28, dose level was a clearly statistically significant predictor of change in phosphorus concentration (P=0.0073).
- The ferric citrate dose level was statistically significant as a predictor of change in the Ca x P product on Day 14 (P=0.0401) and on Day 28 (P=0.0158).
- There were some increases when compared with Day 0 in all ferric citrate groups on both Days 14 and 28 in the mean serum Ca concentration, mean serum iron concentration, ferritin concentration, transferring saturation percentage, and total iron binding capacity (except for a small decrease in mean ferritin concentration on Day 28 and mean transferrin saturation percentage on Study Day 14 in the 4 g/day group), but none of these increases were statistically significant when compared with placebo.

## Dose Ranging Study

<b>Study Report #</b> GBA2-1	<b>Study period</b> 02/13/09-08/24/09
<b>Title:</b> Phase 2 Clinical Study of JTT-751 – Investigation of the Efficacy and Safety of JTT-751 in Hemodialysis Patients –	
<b>EDR Link:</b> \\cdsesub1\evsprod\nda205874\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hyperphosphatemia\5351-stud-rep-contr\gba2-1\gba2-1-body.pdf	
<b>Primary Objectives</b> To investigate the dose-response relationship and safety of JTT-751 at 1.5, 3 and 6 g/day or placebo administered for 28 days in hemodialysis patients.	
<b>Study Design:</b> This was a randomized, double-blind, placebo-controlled, dose-ranging study to assess the effect of ferric citrate on serum phosphorus concentrations in patients with CKD who were undergoing hemodialysis. Patients who met the inclusion/exclusion criteria underwent a three-week washout from all phosphate-binding agents. Patients who had a serum phosphorus $\geq 6.1$ mg/dL and $\leq 10$ mg/dL by the end of this washout period were eligible to be randomized to one of four treatment groups in a ratio of 1:1:1:1 (ferric citrate 1.5, 3, and 6 g/day and placebo, respectively). The primary efficacy variable was the change from baseline to Day 29 in phosphorus concentration. The secondary efficacy variables were listed below. Other variables included change from baseline to Day 29 in iron parameters: serum iron and ferritin concentration and transferrin saturation percentage and total iron binding capacity (IBC).	
<b>Primary Efficacy Endpoint</b> <ul style="list-style-type: none"><li>• Change in serum phosphorus levels from the starting day of administration (Day 1) to the observation day of Week 4 (Day 29)</li></ul>	
<b>Secondary efficacy endpoints</b> <ul style="list-style-type: none"><li>• Change in serum P levels from the starting day of administration (Day 1) to the observation day of Week 2 (Day 15)</li><li>• Change in serum P <math>\times</math> Ca (corrected) levels and serum Ca (corrected) levels from the starting day of administration (Day 1) to the observation day of Week 2 (Day 15) and Week 4 (Day 29)</li><li>• Proportion of subjects achieving the serum P level of <math>\leq 6.0</math> mg/dL</li><li>• Proportion of subjects achieving the serum P level of <math>\leq 5.5</math> mg/dL</li></ul>	
Study drugs (capsules) were taken immediately after the completion of the meal.	
Patients who had been receiving a stable dose of vitamin D or calcitonin preparation for 1 month prior to study enrollment were instructed to maintain their current dose throughout the study.	
Rationale of dose selection: The maximum dose in this study was set to 6g/day, based on previous Phase IIb study where dose of 6 g/day was confirmed to be effective and tolerable. Since this is a study to be conducted in Japan, the sponsor intended to explore the effects at lower doses.	

<b>Code name</b>	JTT-751			
<b>Treatment group</b>	Placebo	1.5 g/day	3 g/day	6 g/day
<b>Method of treatment</b>	Orally administered three times daily immediately after each meal			
<b>Duration of treatment</b>	4 weeks (28 days)			
<b>Investigational products</b>	JTT-751 tablet 500 mg or placebo			
<b>Number of tablets</b>	4 tablets per dose (12 tablets/day)			
<b>Target sample size</b>	42 per group (number of subjects for analyses: 38 per group)			
<b>Efficacy measurements</b>	Serum P and Ca (corrected) levels			
<b>Safety measurements</b>	(1) Subjective symptoms, objective findings (2) Physiological examinations (blood pressure, pulse rate, body temperature, body weight, and standard 12-lead ECG) (3) Laboratory tests			
<b>Others</b>	(1) Endocrine tests (Intact-PTH) (2) Iron-related laboratory tests (serum iron (Fe), ferritin, TIBC, TSAT, CHr) (3) Compliance for the investigational product			

Source: Study report gb2-1, Page 33

### Study medication

	<b>Dosage form</b>	<b>Content</b>	<b>Lot No. of Investigational product</b>	<b>Expiration Date</b>
JTT-751 tablet 500 mg	Tablet	500 mg	GBA2-1	Oct-2009
JTT-751 tablet Placebo	Tablet	—		
JTT-705 tablet 500 mg and Placebo are a reddish yellow film coated tablets, and are identical in appearance.				

Source: Study report gb2-1, Page 42

*Reviewer's note: JTT-751 is a different formulation than the one tested in other dose-response studies.*

### Sampling schedules:

**Serum phosphate and serum calcium:** Screening, Weeks -2, -1, Baseline, Weeks 1, 2, 3, 4 and discontinuation

**Iron parameters** (serum iron, ferritin, total IBC, TSAT and CHr (reticulocyte hemoglobin content): Screening, Baseline, Weeks 1, 2, 3, 4 and discontinuation

### Data Analysis Methods

The change in serum P levels from the starting day of administration (Day 1) to the observation day of Week 4 (Day 29) (plot of the mean change by treatment group) will be assessed using the maximum contrast method. A statistical test will be performed on the difference between placebo and JTT-751 in the amount of change in serum P levels from the starting day of administration (Day 1) to the observation day of Week 4 (Day 29).

**Study population**

No. of Groups	4	<input checked="" type="checkbox"/> Placebo	<input checked="" type="checkbox"/> 1.5 g/day	<input checked="" type="checkbox"/> 3 g/day	<input checked="" type="checkbox"/> 6 g/day
No. of Subject(Completed/enrolled)		35/48	39/49	35/50	20*/45
Age, Mean(range)		63.6(39-87)	60.9(40-77)	58.7(27-78)	57.8(30-78)
Body Weight, kg Mean(range)		58.7 (38.7-78.8)	61.8 (45.2-95.6)	62.1 (36.0-84.5)	63.3 (43.5-90.9)
Baseline serum P, mg/dL, Mean (SD)		7.88 (1.25)	7.74 (1.27)	7.85 (1.31)	7.96 (1.34)

\*: 8 subjects requested withdraw and 9 subjects with serum P levels < 3 mg/dL or > 10 mg/dL

Source: Summarized from study report gba2-1, Page 77, 147

**Results:****Serum Phosphorus levels**

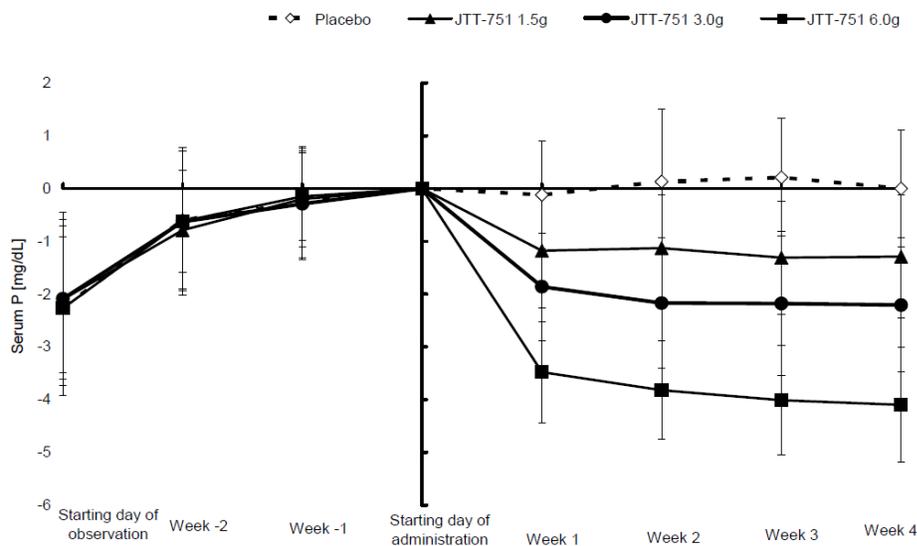
- The amount of change in serum P levels on the observation day of week 4 (Primary efficacy end point) was 0.00 mg/dL in the placebo group, -1.29 mg/dL in the 1.5 g/day group, -2.21 mg/dL in the 3 g/day group, and -4.10 mg/dL in the 6 g/day group.
- The amount of change in the serum P level on the observation day of week 2 (Secondary efficacy end point) was 0.13 mg/dL in the placebo group, -1.13 mg/dL in the 1.5 g/day group, -2.17 mg/dL in the 3 g/day group, and -3.82 mg/dL in the 6 g/day group. All JTT-751 groups showed a decrease in the serum P level that was equal to that found on the observation day of week 4.
- The percentage of subjects who achieved a serum P level of  $\leq 6.0$  mg/dL in the per protocol set (PPS) analysis population on the observation days of week 2 and week 4 was 6.8% and 5.4% in the placebo group, 29.8% and 40.0% in the 1.5 g/day group, 59.1% and 65.8% in the 3 g/day group, and 97.3% and 96.3% in the 6 g/day group, respectively.
- The percentage of subjects who achieved a serum P level of  $\leq 5.5$  mg/dL in the PPS analysis population on the observation days of week 2 and week 4 was 2.3% and 2.7% in the placebo group, 12.8% and 17.5% in the 1.5 g/day group, 45.5% and 50.0% in the 3 g/day group, and 81.1% and 92.6% in the 6 g/day group, respectively.
- Dose response was observed by the sponsor's analysis.

**Table 11-7. Serum P Levels and the Results of Hypothesis Tests on the Observation Day of Week 4 (PPS Analysis Population)**

Treatment group	Descriptive statistics	Serum P		Amount of change	Maximum contrast method	
		Baseline	Week 4	Week 4	Contrast	p-value
Placebo	N	37	37	37	3 1 -1 -3	<0.0001
	Mean	7.75	7.75	0.00	3 -1 -1 -1	<0.0001
	SD	1.17	1.28	1.11	5 1 -3 -3	<0.0001
1.5g/day	N	40	40	40	3 3 -1 -5	<0.0001
	Mean	7.82	6.53	-1.29	1 1 1 -3	<0.0001
	SD	1.12	1.08	1.17		
3g/day	N	38	38	38		
	Mean	7.93	5.72	-2.21		
	SD	1.28	1.40	1.27		
6g/day	N	27	27	27		
	Mean	7.95	3.85	-4.10		
	SD	1.39	1.23	1.09		

unit: mg/dL

Source: Study report gba2-1, Table 11-7, Page 81



**Figure 11-1. Amount of Changes in Serum P levels (PPS Analysis Population)**

Mean ± SD

Source: Study report gba2-1, Figure 11-1, Page 81

**Table 11-11. Serum P Levels and the Results of Hypothesis Tests on the Observation Day of Week 2 (PPS Analysis Population)**

Treatment group	Descriptive Statistics	Serum P		Amount of change	Maximum contrast method	
		Baseline	Week 2	Week 2	Contrast	p-value
Placebo	N	44	44	44	3 1 -1 -3	<0.0001
	Mean	7.88	8.00	0.13	3 -1 -1 -1	<0.0001
	SD	1.25	1.58	1.37	5 1 -3 -3	<0.0001
1.5g/day	N	47	47	47	3 3 -1 -5	<0.0001
	Mean	7.74	6.61	-1.13	1 1 1 -3	<0.0001
	SD	1.27	1.12	1.00		
3g/day	N	44	44	44		
	Mean	7.85	5.68	-2.17		
	SD	1.31	1.13	1.24		
6g/day	N	37	37	37		
	Mean	7.96	4.14	-3.82		
	SD	1.34	1.22	0.94		

unit: mg/dL

Source: Study report gba2-1, Table 11-11, Page 85

**Table 11-13. Achievement Rate of Serum P ≤ 6.0 mg/dL (PPS Analysis Population)**

Week 4		Treatment groups			
		Placebo (N = 37)	1.5 g/day (N = 40)	3 g/day (N = 38)	6 g/day (N = 27)
Serum P ≤ 6.0 mg/dL	Yes	2 (5.4%)	16 (40.0%)	25 (65.8%)	26 (96.3%)
	No	35 (94.6%)	24 (60.0%)	13 (34.2%)	1 (3.7%)
Week 2		Treatment groups			
		Placebo (N = 44)	1.5 g/day (N = 47)	3 g/day (N = 44)	6 g/day (N = 37)
Serum P ≤ 6.0 mg/dL	Yes	3 (6.8%)	14 (29.8%)	26 (59.1%)	36 (97.3%)
	No	41 (93.2%)	33 (70.2%)	18 (40.9%)	1 (2.7%)

Source: Study report gba2-1, Table 11-13, Page 87

**Table 11-15. Achievement Rate of Serum P ≤5.5 mg/dL (PPS Analysis Population)**

Week 4		Treatment groups			
		Placebo (N = 37)	1.5 g/day (N = 40)	3 g/day (N = 38)	6 g/day (N = 27)
Serum P ≤ 5.5 mg/dL	Yes	1 (2.7%)	7 (17.5%)	19 (50.0%)	25 (92.6%)
	No	36 (97.3%)	33 (82.5%)	19 (50.0%)	2 (7.4%)
Week 2		Treatment groups			
		Placebo (N = 44)	1.5 g/day (N = 47)	3 g/day (N = 44)	6 g/day (N = 37)
Serum P ≤ 5.5 mg/dL	Yes	1 (2.3%)	6 (12.8%)	20 (45.5%)	30 (81.1%)
	No	43 (97.7%)	41 (87.2%)	24 (54.5%)	7 (18.9%)

Source: Study report gba2-1, Table 11-15, Page 88

**Serum Calcium (corrected) Levels**

- The amount of change in serum Ca (corrected) levels on the observation days of week 2 and week 4 were -0.03 mg/dL and 0.04 mg/dL in the placebo group, 0.08 mg/dL and 0.12 mg/dL in the 1.5 g/day group, 0.18 mg/dL and 0.11 mg/dL in the 3 g/day group, and 0.25 mg/dL and 0.34 mg/dL in the 6 g/day group, respectively. All the increases were slight changes within the reference range.
- Dose response was not observed by sponsor’s analysis.

**Table 11-21. Amount of Changes in Serum Ca (Corrected) Levels (PPS Analysis Population)**

Treatment group	Descriptive statistics	Week 1	Week 2	Week 3	Week 4
Placebo	N	44	44	41	37
	Mean ± SD	-0.06 ± 0.30	-0.03 ± 0.34	-0.04 ± 0.31	0.04 ± 0.38
1.5 g/day	N	47	47	44	40
	Mean ± SD	0.10 ± 0.30	0.08 ± 0.29	0.20 ± 0.38	0.12 ± 0.34
3 g/day	N	44	44	38	38
	Mean ± SD	0.17 ± 0.31	0.18 ± 0.34	0.13 ± 0.31	0.11 ± 0.29
6 g/day	N	37	37	32	27
	Mean ± SD	0.25 ± 0.33	0.25 ± 0.34	0.25 ± 0.47	0.34 ± 0.32

Unit: mg/dL

Source: Study report gba2-1, Table 11-21, Page 92

**Serum Phosphorus x Calcium(corrected) Levels**

- The amount of change in serum P x serum Ca (corrected) levels on the observation days of week 2 and week 4 were 1.02 mg/dL and 0.29 mg/dL in the placebo group, -9.68 mg/dL and -10.83 mg/dL in the 1.5 g/day group, -18.27 mg/dL and -19.25 mg/dL in the 3 g/day group, and -33.36 mg/dL and -35.57 mg/dL in the 6 g/day group, respectively. The amount of change in serum P x

serum Ca (corrected) levels on the observation days of week 2 and 4 were comparable in all dose groups.

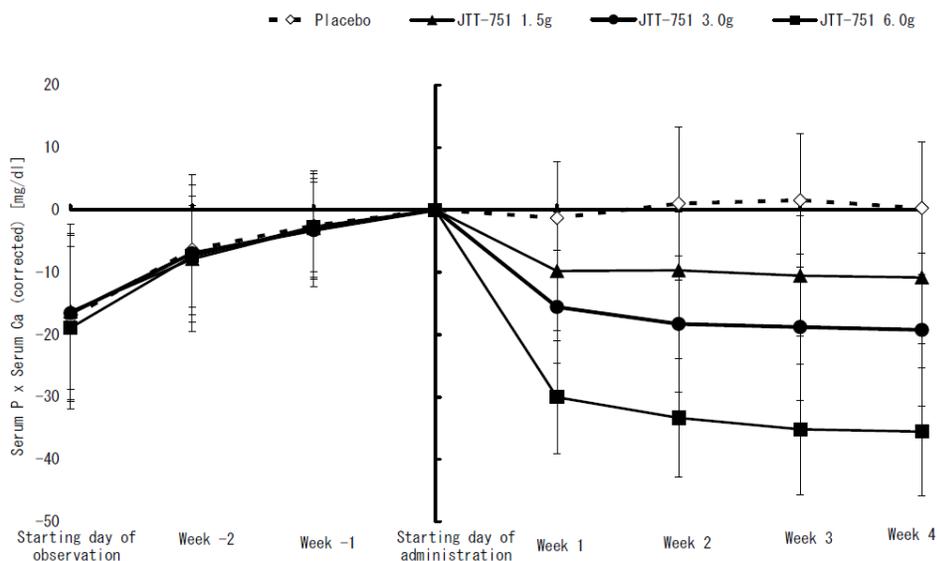
- Dose response was observed by the sponsor’s analysis.
- Compared with the placebo group regarding the test of differences in the mean values, all JTT-751 groups showed significant decreases in serum P x serum Ca (corrected) levels ( $P < 0.0001$  in all comparisons) on both observation days of week 2 and week 4.

**Table 11–24. Serum P x Serum Ca (Corrected) Levels on the Observation Day of Week 4 and Results of Hypothesis Tests by a Maximum Contrast Method (PPS Analysis Population)**

Treatment group	Descriptive statistics	P x Ca		Amount of change	Maximum contrast method	
		Baseline	Week 4	Week 4	Contrast	p-value
Placebo	N	37	37	37	3 1 -1 -3	<0.0001
	Mean	69.40	69.69	0.29	3 -1 -1 -1	<0.0001
	SD	11.23	12.13	10.61	5 1 -3 -3	<0.0001
1.5 g/day	N	40	40	40	3 3 -1 -5	<0.0001
	Mean	70.22	59.39	-10.83	1 1 1 -3	<0.0001
	SD	11.51	11.10	10.55		
3 g/day	N	38	38	38		
	Mean	70.73	51.49	-19.25		
	SD	12.99	12.35	12.27		
6 g/day	N	27	27	27		
	Mean	71.50	35.93	-35.57		
	SD	13.61	11.89	10.27		

Unit: (mg/dL)<sup>2</sup>

Source: Study report gba2-1, Table 11-24, Page 95



**Figure 11-4. Amount of Changes in Serum P x Serum Ca (Corrected) Levels (PPS Analysis Population)**

Source: Study report gba2-1, Figure 11-4, Page 95

**Subset analysis (Baseline phosphate 8 mg/dL, concomitant use of H2 blockers or proton pump inhibitors, concomitant use of vitamin D drugs)**

**Baseline phosphate 8 mg/dL**

- In the JTT-751 groups, the decrease in serum P level tended to be larger as the baseline serum P level became higher.

**Amount of changes in serum P levels on week 4**

Treatment group	Descriptive statistics	Baseline P < 8 mg/mL	Baseline P ≥ 8 mg/mL
Placebo	N	22	15
	Mean ± SD	0.25 ± 1.11	-0.35 ± 1.05
1.5 g/day	N	23	
	Mean ± SD	-0.75 ± 0.88	-2.02 ± 1.14
3.0 g/day	N		
	Mean ± SD	-1.85 ± 0.93	-2.61 ± 1.48
6.0 g/day	N		
	Mean ± SD	-3.71 ± 1.07	-4.46 ± 1.02

Unit: mg/dL

Source: Summarized from study report gba2-1, Tables 11-37 and 11-38, Page 105

**Concomitant use of H2 blockers or proton pump inhibitors**

- There were no obvious differences in the changes in serum P levels among the subgroups divided by the presence or absence of concomitant use of H2 blockers or PPIs.

**Concomitant use of vitamin D drugs**

- There were no obvious differences in the changes in serum P levels among the subgroups divided by the presence or absence of concomitant use of vitamin D drugs.

**Intact-PTH**

- The change in Intact-PTH on the observation day of week 4 was -3.6 pg/dL in the placebo group, -20.2 pg/dL in the 1.5 g/day group, -34.0 pg/dL in the 3 g/day group, and -113.4 pg/dL in the 6 g/day group. The reductions were statistically different from placebo only in the 6 g/day group (P < 0.0001).

**Iron Parameters (Serum iron, Ferritin, Total Iron Binding Capacity (TIBC), Transferrin Saturation Percentage (TSAT), Reticulocyte hemoglobin content (CHr))**

**Serum iron**

- The amount of changes in serum iron (Fe) on the observation day of week 4 was 1.4 µg/dL in the placebo group, 7.7 µg/dL in the 1.5 g/day group, 18.0 µg/dL in the 3 g/day group, and 26.2 µg/dL in the 6 g/day group. Compared with the placebo group in the test of differences in the mean values, there were significant increases in the 3 g/day and 6 g/day groups (P = 0.0363 and P = 0.0005).

**Table 12-13. Amount of Changes in Serum Iron (Fe) (Iron-related Analysis Population)**

Treatment group	Descriptive statistics	Week 1	Week 2	Week 3	Week 4
Placebo	N	47	46	43	39
	Mean ± SD	-4.7 ± 22.4	2.6 ± 20.4	-1.3 ± 22.5	1.4 ± 25.9
1.5 g/day	N	46	46	44	41
	Mean ± SD	13.0 ± 28.6	11.6 ± 34.0	15.5 ± 46.8	7.7 ± 34.0
3 g/day	N	48	47	39	38
	Mean ± SD	21.5 ± 30.1	16.3 ± 27.1	18.5 ± 36.3	18.0 ± 27.9
6 g/day	N	42	37	32	26
	Mean ± SD	22.6 ± 31.6	29.2 ± 42.1	17.0 ± 30.3	26.2 ± 30.9

unit: µg/dL

Source: Study report gba2-1, Table 12-13, Page 134

### **Ferritin**

- The amount of changes in ferritin on the observation day of week 4 was -9.93 ng/dL in the placebo group, 15.16 ng/dL in the 1.5 g/day group, 20.55 ng/dL in the 3 g/day group, and 47.19 ng/dL in the 6 g/day group. Compared with the placebo group regarding the test of differences in the mean values, ferritin levels were increased significantly in all JTT-751 groups ( $P < 0.0001$ , all groups).

**Table 12-14. Amount of Changes in Ferritin (Iron-related Analysis Population)**

Treatment group	Descriptive statistics	Week 1	Week 2	Week 3	Week 4
Placebo	N	47	46	43	39
	Mean ± SD	0.43 ± 17.86	-3.07 ± 21.56	-3.46 ± 19.95	-9.93 ± 20.86
1.5 g/day	N	46	46	44	41
	Mean ± SD	10.45 ± 20.10	11.00 ± 19.80	20.04 ± 28.04	15.16 ± 26.09
3 g/day	N	48	47	39	38
	Mean ± SD	10.56 ± 25.28	10.52 ± 23.65	16.28 ± 28.55	20.55 ± 32.73
6 g/day	N	42	37	32	26
	Mean ± SD	19.12 ± 19.53	23.42 ± 20.75	35.05 ± 23.80	47.19 ± 30.78

unit: ng/mL

Source: Study report gba2-1, Table 12-14, Page 135

### **Total Iron Binding Capacity (TIBC)**

- The amount of changes in TIBC on the observation day of week 4 was 0.2 µg/dL in the placebo group, -12.7 µg/dL in the 1.5 g/day group, -14.9 µg/dL in the 3 g/day group, and -14.7 µg/dL in the 6 g/day group. Compared with the placebo group regarding the test of differences in the mean values, they were reduced significantly in all JTT-751 groups ( $P = 0.0002$  in 1.5 g/day,  $P < 0.0001$  in 3 g/day,  $P < 0.0001$  in 6 g/day).

**Table 12-15. Amount of Changes in TIBC (Iron-related Analysis Population)**

Treatment group	Descriptive statistics	Week 1	Week 2	Week 3	Week 4
Placebo	N	47	46	43	39
	Mean ± SD	-3.7 ± 12.6	2.7 ± 13.7	2.5 ± 18.0	0.2 ± 15.1
1.5 g/day	N	46	46	44	41
	Mean ± SD	-4.4 ± 15.3	-4.1 ± 17.7	-9.4 ± 22.3	-12.7 ± 24.3
3 g/day	N	48	47	39	38
	Mean ± SD	-0.3 ± 17.8	-6.7 ± 17.7	-12.5 ± 21.9	-14.9 ± 23.1
6 g/day	N	42	37	32	26
	Mean ± SD	-7.5 ± 11.5	-7.0 ± 16.4	-12.8 ± 13.0	-14.7 ± 14.2

unit: µg/dL

Source: Study report gba2-1, Table 12-15, Page 137

**Transferrin Saturation (TSAT)**

- The amount of changes in TSAT on the observation day of week 4 was 0.66% in the placebo group, 3.65% in the 1.5 g/day group, 8.63% in the 3 g/day group, and 13.94% in the 6 g/day group. Compared with the placebo group regarding the test of differences in the mean values, they increased significantly in the 3 g/day group and 6 g/day group (P = 0.0025 and P < 0.0001).

**Table 12-16. Amount of Changes in TSAT (Iron-related Analysis Population)**

Treatment group	Descriptive statistics	Week 1	Week 2	Week 3	Week 4
Placebo	N	47	46	43	39
	Mean ± SD	-1.53 ± 8.39	0.76 ± 8.08	-0.46 ± 8.50	0.66 ± 10.09
1.5 g/day	N	46	46	44	41
	Mean ± SD	4.65 ± 9.93	4.53 ± 12.09	6.00 ± 15.51	3.65 ± 12.30
3 g/day	N	48	47	39	38
	Mean ± SD	8.51 ± 12.44	7.03 ± 11.52	8.22 ± 13.72	8.63 ± 11.82
6 g/day	N	42	37	32	26
	Mean ± SD	9.94 ± 11.43	12.44 ± 14.85	9.42 ± 14.06	13.94 ± 13.86

unit: %

Source: Study report gba2-1, Table 12-16, Page 138

**Reticulocyte hemoglobin content (CHr)**

- The amount of changes in CHr on the observation day of week 4 was -0.40 pg in the placebo group, 0.98 pg in the 1.5 g/day group, 1.29 pg in the 3 g/day group, and 0.94 pg in the 6 g/day group. Compared with the placebo group regarding the test of differences in the mean values, CHr were increased significantly in all JTT-751 groups (P = 0.0003 in 1.5 g/day, P < 0.0001 in 3 g/day and P < 0.0001 in 6 g/day).

**Table 12-17. Amount of Changes in CHR (Iron-related Analysis Population)**

Treatment group	Descriptive statistics	Week 1	Week 2	Week 3	Week 4
Placebo	N	45	45	42	38
	Mean ± SD	-0.03 ± 1.79	0.02 ± 1.43	-0.29 ± 1.79	-0.40 ± 1.73
1.5 g/day	N	45	46	44	41
	Mean ± SD	0.88 ± 2.18	1.18 ± 2.51	1.14 ± 2.45	0.98 ± 2.36
3 g/day	N	47	46	38	37
	Mean ± SD	1.42 ± 2.48	1.00 ± 2.52	1.03 ± 2.02	1.29 ± 2.05
6 g/day	N	38	35	30	24
	Mean ± SD	0.92 ± 2.24	1.26 ± 2.18	1.05 ± 1.40	0.94 ± 1.66

unit: pg

Source: Study report gba2-1, Table 12-17, Page 140

**Safety**Death: **None**

- There were no serious adverse events observed in the study.
- The major adverse events were gastrointestinal disorders, such as diarrhea.

**Conclusion**

- The amount of change in serum P levels on the observation day of week 4 was 0.00 mg/dL in the placebo group, -1.29 mg/dL in the 1.5 g/day group, -2.21 mg/dL in the 3 g/day group, and -4.10 mg/dL in the 6 g/day group, and a decreased serum P level showed dose response up to 6 g per day. Similar results were observed on week 2. The phosphate lowering effect is more pronounced in this Japanese study when compared to the two non-Japanese trials (Please refer to the QBR DARRTSed on 6/10/2014 for reasons why this study shows results different from other two studies).
- With respect to serum Ca (corrected) levels in the PPS analysis population, all ferric citrate groups showed increases on week 2 and 4, however, all the increases were slight changes within the reference range and showed no dose response.
- The administration of JTT-751 reduced serum P x serum Ca (corrected), and the dose response was observed. The change was considered to be mainly due to a reduction in serum P.
- The percentage of subjects who achieved the serum P level of ≤6.0 mg/dL and ≤ 5.5 mg/dL in the PPS analysis population on the observation day of week 4 was 96.3% and 92.6%, respectively, in the 6 g/day group.
- Treatment groups that received 3 g/day or more showed significant increases in serum iron (Fe) and TSAT, and all treatment groups showed significant increases in ferritin and CHR, compared to the placebo group. On the other hand, all treatment groups showed significant decreases in TIBC compared to the placebo group.

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/s/  
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JU PING LAI  
07/23/2014

SUDHARSHAN HARIHARAN  
07/23/2014

# Clinical Pharmacology/Biopharmaceutics Review

## Question Based Review (QBR)

PRODUCT (Generic Name):	KRX-0502 (Ferric Citrate)
NDA:	205-874
PRODUCT (Brand Name):	ZERENEX
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	(b) (4) mg tablets (210 mg iron)
INDICATION:	Control of serum phosphorus levels (b) (4) (b) (4) in patients with chronic kidney disease (CKD) on dialysis
NDA TYPE:	Standard
SUBMISSION DATE:	8/7/2013
SPONSOR:	Keryx Biopharmaceuticals, Inc.
REVIEWERS:	Ju-Ping Lai, Ph.D.
TEAM LEADER:	Rajanikanth Madabushi, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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## 1.0 EXECUTIVE SUMMARY

This is an original NDA 205874 submitted by Keryx Biopharmaceuticals, Inc., on August 7, 2013 seeking approval of KRX-0502 (ferric citrate) as a phosphate binder for the control of serum phosphorus levels (b) (4) in patients with chronic kidney disease (CKD) on dialysis.

KRX-0502 is an iron-based phosphate binder. The proposed product is a film-coated tablet ((b) (4) mg) consisting of 210 mg of ferric iron. The submission contains information from three fixed dose dose ranging studies that allows evaluation of dose-response as well as evolution of the drug effect. The dose dependent serum phosphate lowering effect observed in these studies provide supportive evidence for the approval of KRX-0502 as a phosphate binder. Patients should be treated for at least one week before considering dose titration for efficacy. Patients with CKD generally receive multiple drugs for the treatment of underlying co-morbidities; hence there is a need for evaluation of drug interaction potential. Based on the results of the in vitro DDI screening, instruction for use with concomitantly administered drugs was generated.

The clinical significance of the changes in iron parameters was not evaluated in this review. (b) (4)

Since the applicant also use these iron parameter data as a way to evaluate iron bioavailability, OCP has reviewed necessary data and concludes that there are trends for increase in the iron parameters after repeat administration. However, based on the submitted information, it is not possible to quantify the bioavailability of iron from KRX-0502. From a clinical pharmacology perspective, there are no PMRs/PMCs envisioned at this point of time.

## 1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical pharmacology information submitted in NDA 205-874 and has the following recommendations:

- 1) KRX-0502 can be approved as a phosphate binder with the Applicant proposed dose and dosing regimen.
- 2) (b) (4) An agreement on this labeling recommendation with the Applicant is still pending.

## 1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

- A dose-dependent serum phosphorous lowering effect was observed over the range of 1 g/day to 8 g/day. The phosphate lowering effect is more pronounced in the Japanese study when compared to the two non-Japanese trials.
- Near maximum serum phosphate lowering effects of KRX-0502 were seen within 1 week on all doses that showed an effect.

- Seven commonly used classes of drugs in the target population were screened in an attempt to characterize the interaction potential *in vitro*: 1) vitamin D analogues: calcitriol and doxercalciferol; 2) antihypertensive: propranolol, metoprolol, enalapril and amlodipine; 3) anticoagulant/anti-platelet: clopidogrel, warfarin and aspirin; 4) antidiabetics: sitagliptin; 5) antibiotics: doxycycline, levofloxacin; 6) antihyperlipidemics: atorvastatin, fluvastatin and pravastatin; 7) cardiac glycoside: digoxin. Among drugs studied, only doxycycline was found to show extensive binding with KRX-0502 when incubated in aqueous solution that mimics the conditions of the gastro-intestinal (GI) tract with and without the presence of phosphate.

## 2.0 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

**2.1.1** *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?*

**Dosage Form/Strengths:** (b) (4) mg film-coated tablets containing 210 mg of ferric iron

**Indication:** The proposed indication for KRX-0502 (ferric citrate) is for the control of serum phosphorus levels (b) (4) in patients with chronic kidney disease (CKD) on dialysis.

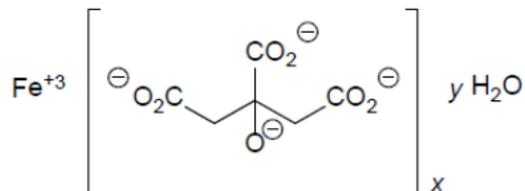
**Pharmacologic Class:** Phosphate binder

**Chemical Name:** Iron (+3), x (1, 2, 3-Propanetricarboxylic acid, 2-hydroxy-), y (H<sub>2</sub>O)

**Chemical formula:** Fe • x (C<sub>6</sub>H<sub>4</sub>O<sub>7</sub>) • yH<sub>2</sub>O; x=0.70-0.87, y=1.9-3.3

**Molecular Weight (FeC<sub>6</sub>H<sub>5</sub>O<sub>7</sub>):** 244.94 (b) (4)

**Chemical structure:**



**Physical Characteristics:**

Solution Parameters
(b) (4)

Source: Modified table from Module 3, drug substance, general properties, table 1, page 1 (3.2.S.1.3)

**Formulation:** KRX-0502 tablets (b) (4) mg contain 210 mg of ferric iron. The to-be marketed formulation was used in the pivotal clinical trial.

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### **2.1.2 What is the proposed mechanism of action?**

KRX-0502, which contains ferric iron as the active ingredient, is a tablet proposed to be taken with meals that binds phosphate in the food content thereby reducing the intake of phosphate. As proposed by the applicant, the iron component of KRX-0502 reacts with dietary phosphate in the GI tract and precipitates phosphate as ferric phosphate. This compound is insoluble and is excreted in the stool. By binding phosphate in the GI tract and decreasing absorption, KRX-0502 lowers the serum phosphate concentration.

### **2.1.3 What are the proposed dosages and route of administration?**

The sponsor's proposed starting dose is (b) (4) 2 tablets orally three times per day with meals. The dose can be increased or decreased by 1 to 2 tablets per day at 2- to 4-week interval. The maximum dose is 12 tablets daily.

## **2.2 GENERAL CLINICAL PHARMACOLOGY**

### **2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?**

There are 16 human study reports submitted to support the dosing and the proposed claim for KRX-0502. 2 Phase II dose-ranging studies (PBB00101 and GBA2-1), 1 Phase III dose-ranging study (KRX-0502-305) and 1 long term safety and efficacy Phase III pivotal study (KRX-0502-304) were provided to support the efficacy and safety of KRX-0502 as a phosphate binder.

In addition, the KRX-0502 clinical pharmacology program also included an *in vitro* DDI screening of 16 drugs that are likely to be concomitantly administered in CKD to evaluate drug interaction potential.

Study KRX-0502-304, KRX-0502-305 and PBB00101 were identified by the sponsor as "adequate and well-controlled" studies that provided the primary support for the efficacy claim for KRX-0502 as a phosphate binder. Study KRX-0502-304 and KRX-0502-305 were conducted under Special Protocol Assessment (SPA) (Special Protocol Agreement letter was DARRTSed on 12/30/2009).

### **Dose-Ranging Studies**

All three studies were randomized, parallel design, multi-center studies in CKD subjects on hemodialysis (thrice-a-week). The primary efficacy variable was the change in serum phosphorus level from baseline to the end of the treatment period (4 weeks).

Study KRX-0502-305 (N = 151) was open-label, evaluated the dose-response relationship and efficacy of fixed doses of 1, 6, and 8 g/day of KRX-0502 in 1 g (b) (4)

Study PBB00101 (N = 111) was a double-blind study and evaluated doses of 2, 4, and 6 g/day of pharmaceutical-grade ferric citrate in capsules.

Study GBA2-1 (N = 192) was also a double-blind, comparator study, conducted in Japan and sponsored by Japan Tobacco, Inc. (JT). This study evaluated the dose-response relationship and safety of 1.5, 3, and 6 g/day JTT-751 in 500 mg tablets.

### **Pivotal Study**

Study KRX-0502-304 was a multicenter, randomized, open-label, 58-week study, which evaluated the safety and efficacy of KRX-0502 1-g caplets with a starting dose of 6 g/day, titrated in the range of 1 to 12 caplets /day in subjects with CKD on dialysis. The design included: 1) a washout period of up to 2 weeks followed by 2) a 52-week safety assessment period (comparing KRX-0502 to active controls of sevelamer carbonate and/or calcium acetate) and then 3) a 4-week efficacy assessment period (comparing KRX-0502 to placebo in the patients assigned to KRX-0502 who successfully completed the safety assessment period). The primary efficacy endpoint in this study was the change from Week 52 in serum phosphorus levels to Week 56. A total of 441 subjects were randomized, and 438 were treated with study drug (289 subjects with KRX-0502 and 149 subjects with active control). Doses for both active control and KRX-0502-treated subjects were titrated depending on serum phosphorus levels, with an overall mean KRX-0502 dose at the end of the study of 8.78 caplets/day (median=9.00 g/day; range of 0 to 12 g/day).

#### **2.2.2 *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?***

The Kidney Disease Outcome Quality Initiative (KDOQI) guidelines (Guideline 4) state that, when the dietary phosphate restriction is inadequate to control serum levels of phosphorous and /or PTH, the second line of therapy is the administration of phosphate binders (Guideline 5). Thus, dietary phosphate binders have been one of the mainstays of treatment in CKD patients with kidney failure and those treated with hemodialysis or peritoneal dialysis. The aim of treatment with dietary phosphate binders is to achieve control of serum phosphorous levels within the guideline specified range of 3.5 and 5.5 mg/dL (Guideline 3) in CKD patients. Consequently, the primary efficacy measure used in the evaluation of effectiveness is the change in serum phosphate. Serum phosphate levels were measured in local as well as a central laboratory by standard validated clinical laboratory methods.

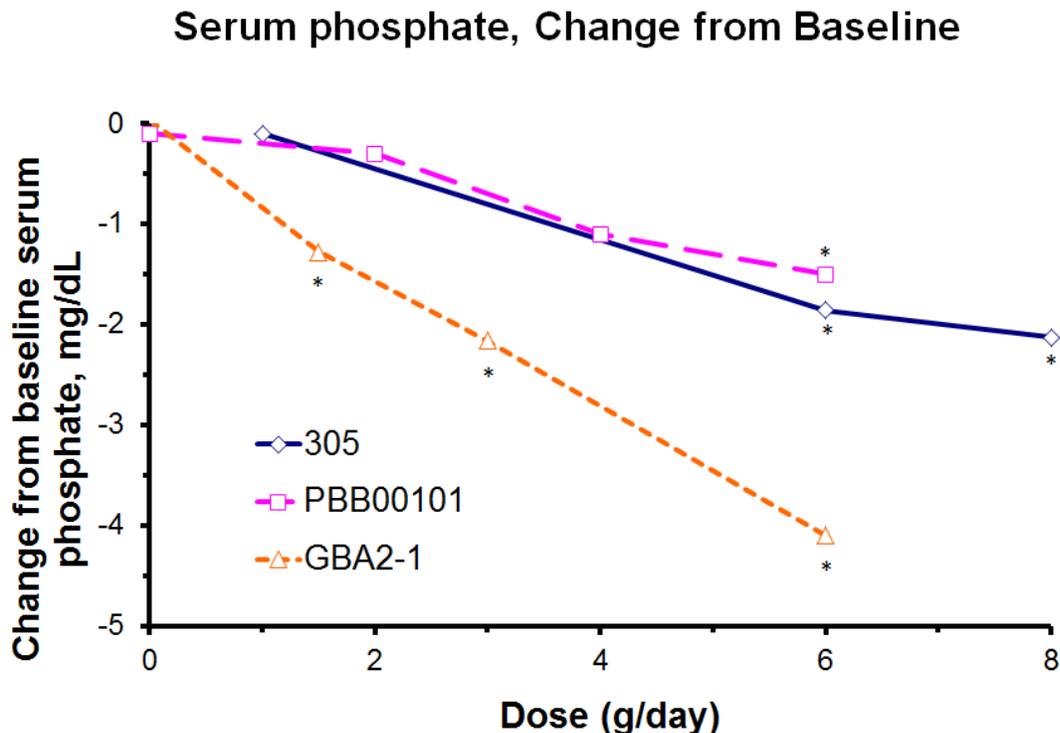
#### **2.2.3 *What are the characteristics of exposure-response (E-R) relationships for efficacy and safety?***

The three fixed-dose, dose-ranging studies (0 (placebo), 1 g/day up to 8 g/day) provided dose-response information to support the dose selection as well as supportive evidence for drug effect.

A dose dependent effect in lowering serum phosphate was observed in all three studies (Figure 1). Study KRX-0502-305 (US) and PBB00101 (US and Taiwan) showed similar dose-response relationship where doses of 6 g/day or higher demonstrated significant reduction in serum

phosphate when compared to placebo or lowest dose. Study GBA2-1 which was conducted in Japan showed a steeper dose-response relationship where dose as low as 1.5 g/day showed significant reduction in serum phosphate.

Figure 1: Change from Baseline in Serum Phosphorus Levels (mg/dL) at End of Treatment



\* p<0.05 compared to placebo or lowest dose within the study

The E-R relationship was not conducted in this submission as the drug is intended to work in the GI tract and there is minimal absorption of the product.

### Dose-Response for Safety / Drop-out

No trend of dose dependent AEs and drop-outs was observed in study PBB00101 where doses of 0, 2, 4, 6g/day were evaluated. In study KRX-0502-305, the overall AEs in 6g/day (82.7%) and 8g/day (85.4%) were similar but higher than that in 1g/day (66.7%). A dose related increase in drop out due to AEs was observed with 3.9%, 5.8% and 16.7% in 1, 6 and 8g/day groups, respectively.

In study GBA2-1, the overall AEs in 1.5g/day (57.1%), 3g/day (50.0%) and 6g/day (55.6%) were similar but slightly higher than placebo (47.9%). No dose related trend on drop outs due to AEs were observed.

Based on these findings, dose of 6g/day did not show concerns on safety or AEs when compared to lower doses or placebo. Only 8g/day dose seems to cause significant AEs and drop outs.

## Is the proposed dose and dosing regimen acceptable?

A starting dose of 6 g/day consistently showed effects on lowering serum phosphate in all fixed-dose studies. Doses as low as 4 g/day in study PBB00101 also showed phosphate lowering effects. In the pivotal trial, a starting dose of 6g/day followed by titration to effect demonstrated efficacy. Further, very few subjects ( $n < 20$ )<sup>1</sup> required down titration in this study. Based on this information, a starting dose of 6g/day is acceptable. However, the Applicant is proposing (b) (4)



In most of the studies, near maximum effect for phosphate lowering was observed after 7 days of treatment (see Figures 3 & 4 on Page 13). Hence duration of at least 1 week of treatment before considering titration to higher dose is necessary. The Applicant is proposing titration every 2 – 4 weeks which is acceptable.

## Why are the results from the Japanese study different from the other two studies?

The impact of baseline serum phosphate, time of KRX-0502 in relation to meals, formulation differences, body size and dietary phosphate intake were evaluated in an attempt to understand the reasons for the differences in the results between the Japanese study and the other studies.

- 1) Baseline serum phosphate: The baseline level of serum phosphate in the three fixed-dose studies was reasonably similar between studies. The mean baseline level of serum phosphate in PBB00101, KRX-0502-305, and GBA2-1 were ~7.2, ~7.4 and ~7.8 mg/dL, respectively. The small numerical differences are unlikely to explain the findings.
- 2) Time of binder in relation to meals: Study protocol KRX-0502-305 indicated that the binder was to be taken “at or within one hour of the meal” whereas in Japanese study, the binder was to be taken immediately after completion of meals. While the one hour difference might contribute to the different effect size, no detailed information on the exact time of binder administration in study KRX-0502-305 is available to figure out the average time of administration of the binder in relation to meals. Further, in study PBB00101, binders were to be taken within 10 minutes of completing meals which is closer to Japanese study, the treatment differences between the studies exist. Hence the time of binder in relation to meals seem unlikely to explain the effect size differences.
- 3) Formulation differences: In the Japanese study 500 mg tablets were used compared to 1 g (b) (4) in study KRX-0502-305. The strength difference is not expected to contribute to the effect size difference. The formulation difference could play some role on the effect size. Therefore an information request (IR) was sent to the Applicant for clarification of the drug substance and formulations used between studies in US and Japan.

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<sup>1</sup> Source: from available dose information in dataset EX, provided by the sponsor

Based on the sponsor's submission on April 23, 2014 in response to the IR # 32, drug substance used in Japanese studies and US studies were essentially the same; (b) (4)



- 4) Lower body weight in Asian population: An attempt was made by the Applicant to compare the effect size and body weight in study PBB00101 where approximately half of the subjects were Taiwanese and half of the subjects were from US. A greater than 2 fold higher effect size was seen in Taiwanese when compared to US population at the same dose of 6 g/day (-2.35 mg/dL vs. -1.09 mg/dL) (Table 1). Approximately 30 kg lower body weight was observed in Taiwanese when compared to that of US population (62 kg vs. 94 kg) (Table 1). Similar difference was also seen when comparing study KRX-0502-305 (US) and GBA2-1 (Japan) implicating a role for body weight in explaining the difference in the effect size between Japanese and US studies. However, there is no clear biological basis for considering body weight for a product that exhibits pre-systemic effects.

Table 1 Comparison of body weight and serum phosphorus change between US and Asian subjects on the 6 g/day dose- Fixed-dose studies

		PBB00101		
Time Point	Statistics	US (N=18)	Taiwan (N=15)	Difference (US-Taiwan)
Weight at screening or baseline	Mean, kg	94	62	32
Serum phosphorus change from baseline	Mean (SD), mg/dL	-1.09 (1.65)	-2.35 (1.26)	1.26

Source: summarized from ISE, table37, page 151

- 5) Lower dietary phosphate intake in Asian population: Also another attempt by the Applicant was made to compare dietary phosphate intake in study PBB00101. There was a generally lower dietary phosphate intake observed for Taiwanese in study PBB00101 (Table 2). While considering dietary differences the most plausible factor, the differences between the populations is not that significant to explain the differences by itself.

Table 2 Comparison of serum phosphorus change and dietary phosphate intake between US and Asian subjects on the 6 g/day dose- Fixed-dose studies

		PBB00101		
Dietary phosphate intake		US (N=64)	Taiwan (N=52)	Difference (US-Taiwan)
Dialysis Day	Mean, mg/dL	910.02	804.14	105.88
Non-dialysis Day	Mean, mg/dL	908.62	951.42	-42.8
Weekend Day	Mean, mg/dL	902.46	833.14	69.32

Source: summarized from ISE, table 35, page 150

Based on the above information, a combination of body weight and dietary phosphate intake differences might contribute to the differences in the efficacy observed across the studies.

#### 2.2.4 What are the PK characteristics of KRX-0502?

No conventional clinical pharmacology studies were conducted in this submission as it is expected to have only minimal absorption of iron.

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##### 2.2.4.1 What are the characteristics of drug absorption?

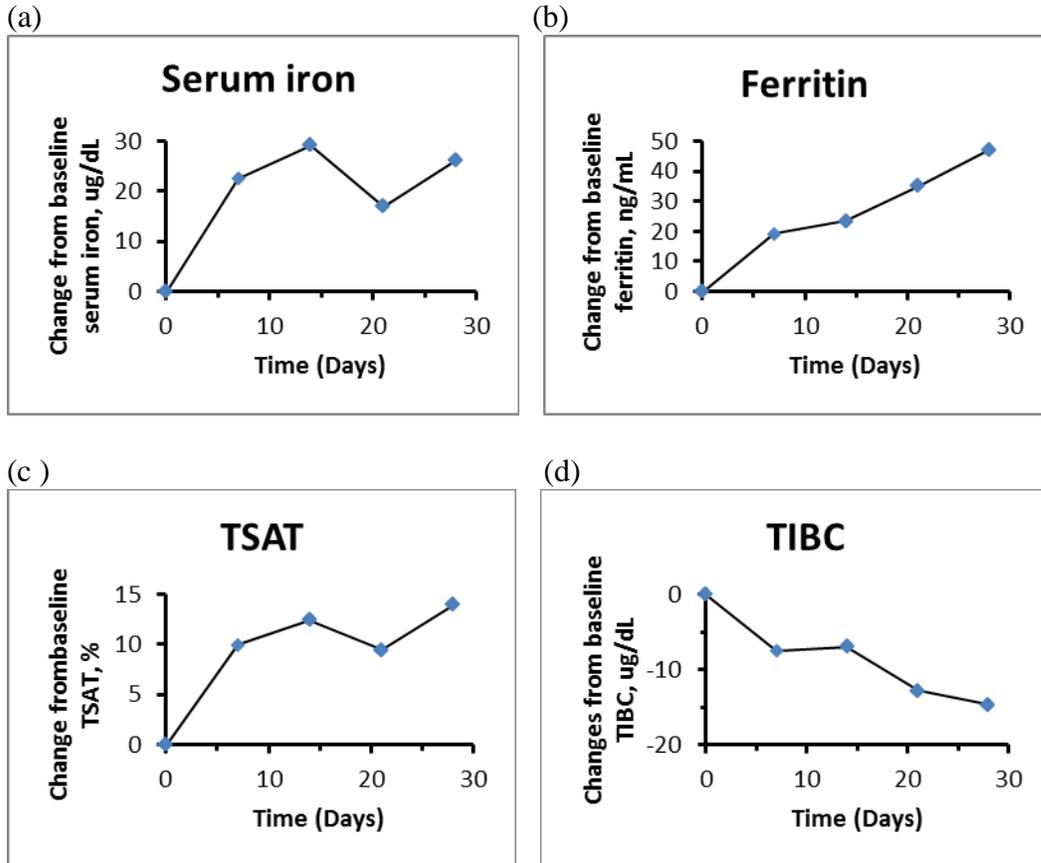
KRX-0502 is expected to be minimally absorbed. No clinical mass balance study was conducted in this program. (b) (4)

Hematology Product (DHP) was consulted (b) (4)

Division of  
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this review is to understand the change of rate and extent of the iron parameters as a way to evaluate the bioavailability of iron after KRX-0502 administration. While IV iron was allowed in long term studies and dose of KRX-0502 was titrated in most studies, iron parameter changes could be confounded by these factors, hence evaluation was done in studies where dose of KRX-0502 was fixed and IV iron was prohibited. Since multiple studies showed similar trend on iron parameter changes and study GBA2-1 has the richest data (weekly data for all four parameters) available, data for short term effect (28 days) from this study was shown below. From this fixed-dose study, it appears that close to plateau have been reached at the first time point observed (7 days) for serum iron and TSAT while ferritin was still increasing and TIBC was still decreasing over 28 days (Figure 2). Biweekly iron parameter data are also available in other studies. Although there is a possibility that the effects in study GBA2-1 might be different, the change from from baseline ferritin level on Day 28 appears similar to that in study PBB00101.

Figure 2: Time course of iron parameter (changes from baseline) over 28 days. (a) serum iron, (b) ferritin, (c) TSAT and (d) TIBC.

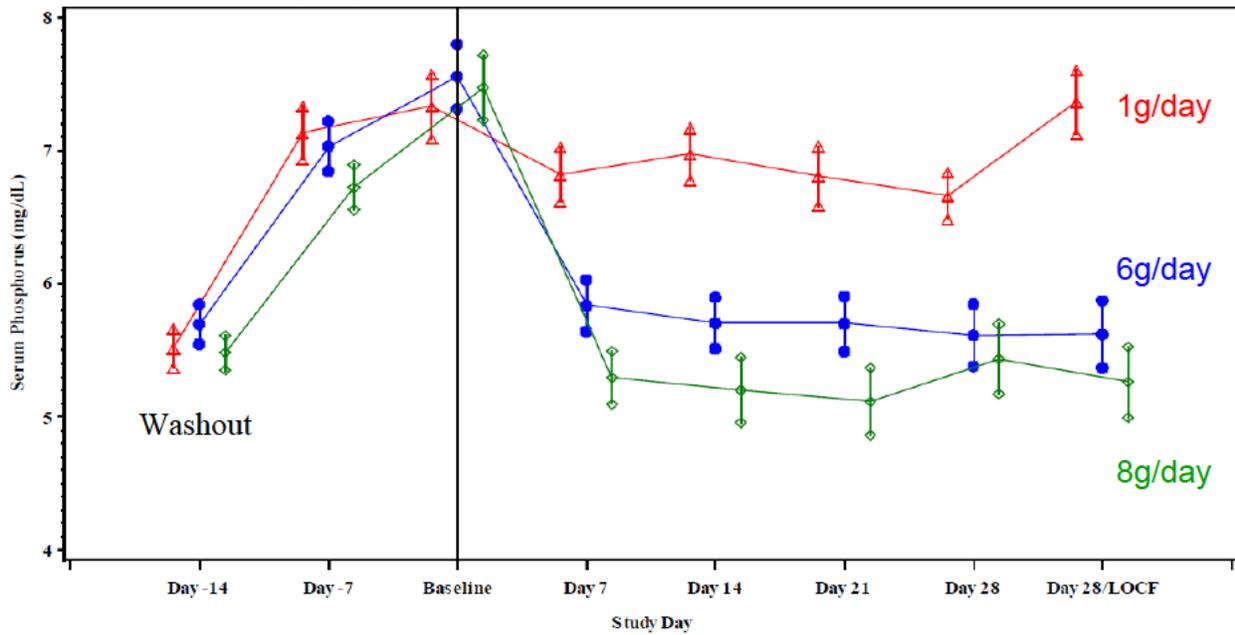


These data confirmed that there was iron absorption from KRX-0502. The clinical significance of these changes [REDACTED] <sup>(b) (4)</sup> was evaluated by medical officer and consulted by DHP.

### 2.2.5 What are the PD characteristics of the drug?

As mentioned previously, pharmacodynamic activity of KRX-0502 was mainly assessed by the serum phosphate level changes from baseline. The decreased of serum phosphate levels were consistently observed in multiple clinical studies. Based on the time course of the serum phosphate lowering effects observed in the phase III study (KRX-0502-305), it can be clearly seen that near maximum effects following a fixed dosing are achieved by 1 week (Figure 3).

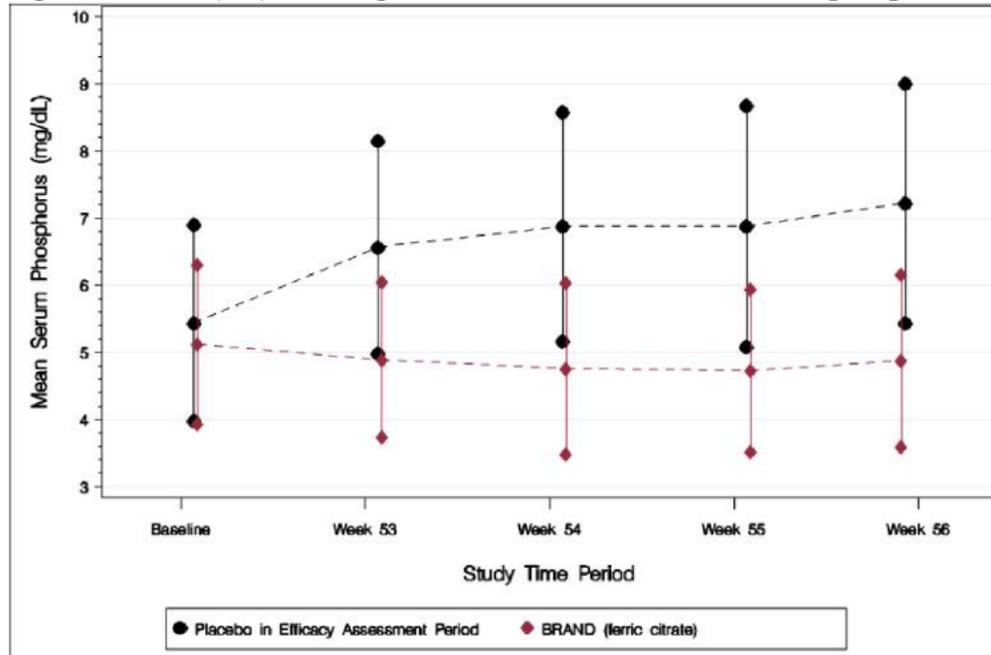
Figure 3: Mean serum phosphorus levels over time



Source: Study report KRX-0502-305, Figure 12.1.1, page 47

From the pivotal trial (KRX-0502-304), after withdrawal of the KRX-0502, serum phosphate levels also increased quickly. Close to maximum effect was observed as soon as 1 week of withdrawal (Figure 4).

Figure 4: Mean (SD) of change from week-52 baseline in serum phosphorus by week



Source: Study 304 CSR, Figure 14.2.1.1

FAS=Full Analysis Population; SD=standard deviation.

This would support the titration scheme to a higher or lower dose every week though the data also support the sponsor's proposal of a 2- to 4-week interval based on what was done in the pivotal trial.

### **2.3 INTRINSIC FACTORS**

Intrinsic factors are not expected to impact the availability of KRX-0502 at the site of action and hence were not evaluated.

### **2.4 EXTRINSIC FACTORS**

It is expected to have minimal absorption of iron from KRX-0502. No conventional clinical pharmacology studies were conducted in this submission. The focus in this NDA was on the potential of KRX-0502 to bind concomitant drugs in the GI tract and reduce the bioavailability of the concomitant drugs.

#### ***2.4.1 Is KRX-0502 a substrate, inhibitor or inducer of CYP enzymes and/or transporters?***

The potential of KRX-0502 to be a substrate, inhibitor or inducer of CYP enzymes and/or transporters is expected to be minimal and were not evaluated in this NDA.

#### ***2.4.2 Is there an in vitro basis to suspect drug-drug interaction?***

Yes. *In vitro* studies were conducted in phosphate buffer and aqueous solution which mimic the physico-chemical conditions of the GI tract in both fed condition and worst case scenario of KRX-0502 to bind commonly concomitant drugs. The media were incubated at pH 4.5 and 6.8 at 37°C for 6 hours. The amount of the concomitant drug remaining at the end of the incubation was measured to evaluate the extent of binding to KRX-0502.

Extensive binding (70% at pH 4.5 and 89% at pH 6.8) were observed for doxycycline. This may be avoided with spacing because doxycycline is virtually completely absorbed after oral administration and T<sub>max</sub> is ~1-2 hours with delayed absorption with food. When administered in fasted condition, gastric emptying generally occurs within 0.5 to 1 hour where most of the drug moved to the small intestine 1 hour after administration. Therefore spacing by at least 1 hour would minimize the interaction potential between doxycycline and ferric citrate (with meal). Hence the recommendation for doxycycline is to take them at least 1 hour before Zenerex.

No interactions were observed for 1) vitamin D analogues: calcitriol and doxercalciferol; 2) antihypertensive: propranolol, metoprolol, enalapril and amlodipine; 3) anticoagulant/anti-platelet: clopidogrel, warfarin and aspirin; 4) antidiabetics: sitagliptin; 5) antibiotics: levofloxacin; 6) antihyperlipidemics: atorvastatin, fluvastatin and pravastatin; 7) cardiac glycoside: digoxin. Hence these drugs can be used with KRX-0502 and no dose adjustment is warranted.

## 2.5 GENERAL BIOPHARMACEUTICS

### 2.5.1 *What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?*

The final to-be-marketed formulation was used in the pivotal clinical trial. In addition, the product is only minimally absorbed. Hence, bioequivalence studies were not conducted.

## 2.6 ANALYTICAL

### 2.6.1 *What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?*

The assay methods for drugs tested in the *in vitro* DDI studies are acceptable. System suitability, linearity, accuracy, precision, specificity (non-interference), PQL (Practical Quantitation Limit) and range of each drug were evaluated. Concentrations of drugs in *in vitro* testing media were determined using reverse phase high performance liquid chromatography (RP-HPLC) method.

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/s/  
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JU PING LAI  
06/09/2014

RAJANIKANTH MADABUSHI  
06/10/2014

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 205874	<b>Biopharmaceutics Reviewer:</b> Elsbeth Chikhale, PhD	
<b>Submission Date:</b>	August 6, 2013		
<b>Division:</b>	Division of Cardio Renal Products	<b>Biopharmaceutics Team Leader:</b> Angelica Dorantes, PhD	
<b>Applicant:</b>	Keryx Biopharmaceuticals, Inc.	<b>Acting Supervisor:</b> Richard Lostritto, PhD	
<b>Trade Name:</b>	Zenerex	<b>Date Assigned:</b>	August 7, 2013
<b>Generic Name:</b>	Ferric Citrate Tablets	<b>Date of Review:</b>	April 2, 2014
<b>Indication:</b>	to control of serum phosphate levels (b)(4) in patients with chronic kidney disease on dialysis	<b>Type of Submission:</b> 505(b)(2) Original New Drug Application	
<b>Dosage form/ strengths</b>	Tablets/ (b)(4) mg ferric citrate/tablet		
<b>Route of Administration</b>	Oral		
<b><u>SUMMARY:</u></b>			
<b><i>Submission:</i></b>			
<p>This NDA is submitted via the 505(b)(2) regulatory pathway, because the Applicant is referencing the published literature for data from non-clinical reproductive toxicology, carcinogenicity and mutagenicity studies. The proposed drug product is indicated for the control of serum phosphate levels (b)(4) in patients with chronic kidney disease on dialysis. The ferric citrate drug substance is (b)(4)</p> <p>The principal pharmacodynamic action of ferric citrate (phosphate binding) occurs in the GI tract, without systemic absorption. Therefore, the Applicant did not conduct any standard, short-term bioavailability or bioequivalence studies.</p>			
<b><i>Review:</i></b>			
<p>The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:</p> <ol style="list-style-type: none"> <li>1) the dissolution methodology,</li> <li>2) the dissolution acceptance criterion, and</li> <li>3) the bridging of the different formulations used in the Phase 2 and 3 studies</li> </ol>			

**RECOMMENDATION:**

1. The following dissolution method is acceptable:

Dosage Form	USP Apparatus	Speed (rpm)	Dissolution Medium
Tablets	USP 2 (Paddle)	100	900 mL EDTA at 37°C

2. The proposed dissolution acceptance criterion of Q<sup>(b) (4)</sup>% at <sup>(b) (4)</sup> minutes was not supported by the data and was not accepted. Based on the overall dissolution data from the clinical and registration batches a dissolution acceptance criterion of Q=<sup>(b) (4)</sup>% at 45 minutes was recommended and agreed upon with the Applicant.
3. The change in formulation <sup>(b) (4)</sup>

does not require bridging <sup>(b) (4)</sup>

From the Biopharmaceutics perspective, NDA 205874 for Ferric Citrate Tablets containing <sup>(b) (4)</sup> mg ferric citrate/tablet is recommended for **APPROVAL**.

**Elsbeth Chikhale, Ph.D.**

Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Angelica Dorantes, Ph.D.**

Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

**BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES**

This NDA is submitted via the 505(b)(2) regulatory pathway, because the Applicant is referencing the published literature for data from non-clinical reproductive toxicology, carcinogenicity and mutagenicity studies. The proposed drug product is indicated for the control of serum phosphate levels (b) (4) in patients with chronic kidney disease on dialysis. The ferric citrate drug substance is (b) (4)

The principal pharmacodynamic action of ferric citrate (phosphate binding) occurs in the GI tract, without systemic absorption. Therefore, the Applicant did not conduct any standard, short-term bioavailability or bioequivalence studies. The proposed formulation is as follows:

Component	Quality Standard	Function	Target Quantity (Unit Dosage)	Range %w/w
Ferric citrate	In-house	Active ingredient	(b) (4) mg	(b) (4)
Pre-gelatinized starch	NF, Ph.Eur.	(b) (4)	(b) (4)	(b) (4)
Calcium stearate	NF			
(b) (4)	USP, Ph.Eur.			
(b) (4)	N/A			
(b) (4)	N/A			
(b) (4)	In-house			
(b) (4)	USP, Ph. Eur.			
Coated total <sup>b</sup> (b) (4)	N/A			

(b) (4) N/A=not applicable; NF=National Formulary; Ph.Eur.=European Pharmacopoeia; USP=United States Pharmacopoeia.

**DISSOLUTION METHOD:**

The proposed dissolution method is: Apparatus 2 (paddle), 900 mL ethylenediaminetetraacetic acid (EDTA) at 37 °C, at 100 rpm.

The NDA submission did not include the dissolution method development report, nor the analytical validation report for the assay used to evaluate the dissolution samples.

The following comments were sent to the Applicant as an information request dated 10/1/13.

1. *Submit the dissolution method development report which should include the following:*

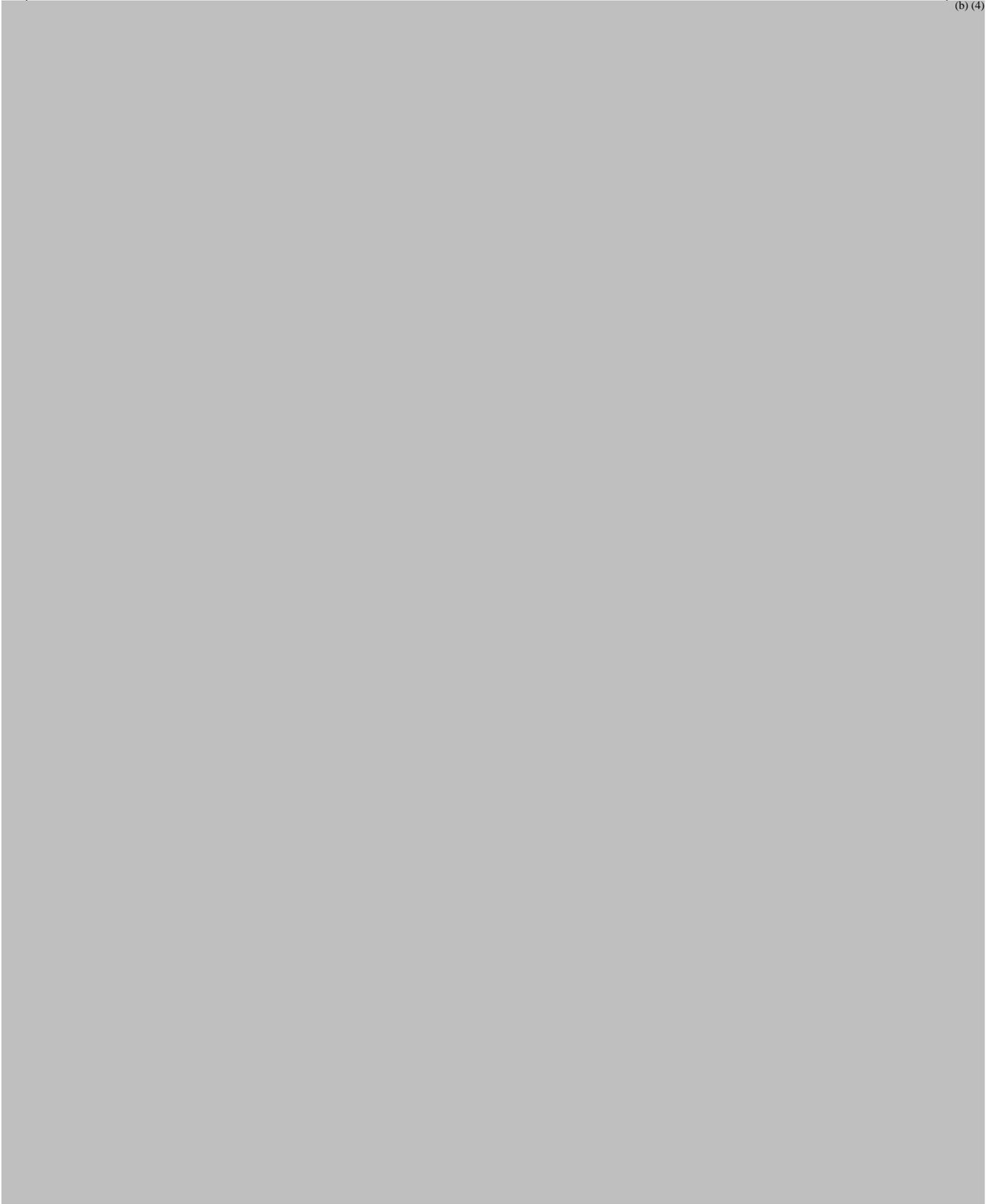
(b) (4)

2. *Your NDA submission only included the dissolution-stability data for the (b) (4) minutes time point. Submit the complete dissolution profile (b) (4) data for the stability registration batches. If you have not collected dissolution profile data at all the time points, please start immediately collecting it for the stability batches and submit it to FDA as soon as it becomes available.*
3. *The analytical method validation report "METHVAL-0132-R-A-02 Addendum" for the dissolution test mentioned in section 3.2.P.5.3 could not be located. Submit this report or indicate where the report is located in your NDA.*

The Applicant provided a response in an amendment dated 10/4/13, providing a dissolution method development report in response to question 1, and responses with the requested information for questions 2 and 3.

The selection of the proposed dissolution method is based on the following information:

(b) (4)



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**BRIDGING OF THE DIFFERENT FORMULATIONS USED IN THE PHASE 2 and 3 STUDIES:**

**History of drug products used in Phase 2, Phase 3, and Long-term Stability Studies:**

Type of Study	KRX-0502 Product
Phase 2 study (Study 201) and stability studies	(b) (4) capsules filled with 375-mg drug substance manufactured by (b) (4) at (b) (4) kg scale
Phase 2 study (Study 202) and stability studies	1 g caplets with (b) (4) % w/w calcium stearate manufactured by (b) (4) at (b) (4) kg scale
Phase 2 study (Study 204 <sup>a</sup> ) and stability studies	1 g caplets with (b) (4) % w/w calcium stearate manufactured by (b) (4) at (b) (4) and/or (b) (4) kg scale
Phase 3 clinical studies (Study 304 and Study 305) and stability studies	1 g (b) (4) with (b) (4) % w/w calcium stearate through (b) (4) (b) (4) manufactured by (b) (4) at (b) (4) kg scale
Phase 3 clinical studies (Study 304), stability studies, and manufacturing process validation	1 g caplets with (b) (4) % w/w calcium stearate (b) (4) starting (b) (4) manufactured by (b) (4) (b) (4) at (b) (4) kg scale
Phase 3 clinical studies (Study 307 <sup>a</sup> ) and stability studies	1 g caplets with (b) (4) % w/w calcium stearate (4 lots) and with (b) (4) % w/w calcium stearate (2 lots) manufactured by (b) (4) (b) (4) at (b) (4) and/or (b) (4) kg scale

Sources: [Module 3.2.P.2.2, Table 6](#); Individual study Clinical Study Reports.

<sup>a</sup> Study KRX-0502-204 and Study KRX-0502-307 (Study 204 and Study 307, respectively) are ongoing studies. NDA=New Drug Application; w/w=weight/weight.



(b) (4)

**RECOMMENDATION:**

1. The following dissolution method is acceptable:

Dosage Form	USP Apparatus	Speed (rpm)	Dissolution Medium
Tablets	USP 2 (Paddle)	100	900 mL EDTA at 37°C

2. The proposed dissolution acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at  $\frac{(b)}{(4)}$  minutes was not supported by the data and was not accepted. Based on the overall dissolution data from the clinical and registration batches a dissolution acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at **45 minutes** was recommended and agreed upon with the Applicant.
3. The change in formulation (b) (4)

[Redacted text block]

From the Biopharmaceutics perspective, NDA 205874 for Ferric Citrate Tablets containing (b) (4) mg ferric citrate/tablet is recommended for **APPROVAL**.

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/s/  
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ELSBETH G CHIKHALE  
04/02/2014

ANGELICA DORANTES  
04/02/2014

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	205874	Brand Name	TBD
OCP Division (I, II, III, IV, V)	I	Generic Name	Ferric Citrate
Medical Division	Cardio-Renal	Drug Class	Phosphate binder
OCP Reviewer	Ju-Ping Lai	Indication(s)	Control of serum phosphorus levels (b) (4) in patients with chronic kidney disease (CKD) on dialysis.
OCP Team Leader	Rajanikanth Madabushi	Dosage Form	(b) (4)
Pharmacometrics Reviewer		Dosing Regimen	<b>Starting dose:</b> (b) (4) 2 g orally 3 times per day with meals <b>Titration:</b> Doses can be increased or decreased by 1 to 2 g per day at 2- to 4-week intervals as needed to maintain serum phosphorus at recommended target levels (3.5 to 5.5 mg/dL), up to a maximum dose of 12 g daily. (b) (4)
Date of Submission	8/7/2013	Route of Administration	Oral
Estimated Due Date of OCP Review	4/7/2014	Sponsor	Keryx Biopharmaceuticals, Inc.
Medical Division Due Date	4/7/2014	Priority Classification	Standard
PDUFA Due Date	6/7/2014		

***Clin. Pharm. and Biopharm. Information***

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:	X	11		Evaluating iron parameters
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	3 studies (42 drugs)		Screening for potential DDIs
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:	X	3		KRX-0502-202 (New formulation, caplet), PBB00101 (Dose-ranging), GBA2-1 (Dose-ranging) 304 (long-term extension), 305 (4 weeks, dose-response)
Phase 3:	X	2		
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>		10		
<b>Total Number of Studies</b>		29		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	TBM product used for 2 Phase III pivotal trials
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	PK not representative of iron absorption; iron parameters used.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	Standard Lab measurements for iron parameters
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?			X	PK not representative of iron absorption; iron parameters used.
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

<b>General</b>				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

    Yes    

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Ju-Ping Lai	09/30/13
Reviewing Clinical Pharmacologist	Date

Raj Madabushi	09/30/13
Team Leader/Supervisor	Date

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JU PING LAI  
10/01/2013

RAJANIKANTH MADABUSHI  
10/02/2013

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

<b>NDA Number</b>	205874
<b>Submission Date</b>	8/7/13
<b>Product name, generic name of the active</b>	Ferric Citrate Tablets
<b>Dosage form and strength</b>	Tablets – (b) (4) mg ferric citrate/tablet
<b>Route of Administration</b>	Oral
<b>Applicant</b>	Keryx Biopharmaceuticals, Inc.
<b>Clinical Division</b>	Division of Cardio Renal Products
<b>Type of Submission</b>	Original NDA – 505(b)(2)
<b>Biopharmaceutics Reviewer</b>	Elsbeth Chikhale, Ph.D.
<b>Biopharmaceutics Team Leader</b>	Angelica Dorantes, Ph.D.

### Biopharmaceutics Summary

#### General Summary

This NDA is submitted via the 505(b)(2) regulatory pathway, because the Applicant is referencing the published literature for data from non-clinical reproductive toxicology, carcinogenicity and mutagenicity studies. The proposed drug product is indicated for the control of serum phosphate levels (b) (4) in patients with chronic kidney disease on dialysis. The ferric citrate drug substance is (b) (4)

The principal pharmacodynamic action of ferric citrate occurs in the GI tract, without systemic absorption. Therefore, the Applicant did not conduct any standard, short-term bioavailability or bioequivalence studies. The proposed formulation is as follows:

Component	Quality Standard	Function	Target Quantity (Unit Dosage)	Range %w/w
Ferric citrate	In-house	Active ingredient	(b) (4)	(b) (4)
Pre-gelatinized starch	NF, Ph.Eur.		(b) (4)	(b) (4)
Calcium stearate	NF		(b) (4)	(b) (4)
(b) (4)	USP, Ph.Eur.		(b) (4)	(b) (4)
	N/A		(b) (4)	(b) (4)
	N/A		(b) (4)	(b) (4)
	In-house		(b) (4)	(b) (4)
	USP, Ph. Eur.		(b) (4)	(b) (4)
	N/A		(b) (4)	(b) (4)

LOD=loss on drying; N/A=not applicable; NF=National Formulary; Ph.Eur.=European Pharmacopoeia; USP=United States Pharmacopoeia.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Development formulation:

Component	Function	Quantity per Unit Dose (mg/caplet)	Range (%w/w)
Ferric citrate	Drug substance	(b) (4)	(b) (4)
Pregelatinized starch	(b) (4)	(b) (4)	(b) (4)
Calcium stearate	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Formulations used in phase 2 and 3 studies:

Type of Study	Ferric Citrate Product
Phase 2 clinical and stability studies	(b) (4) capsules filled with 375 mg drug substance and one lot of 1 g caplets with (b) (4) manufactured by (b) (4) at (b) (4) kg scale
Phase 3 clinical trials and stability studies	1 g caplets with (b) (4) through (b) (4) manufactured by (b) (4) at (b) (4) kg scale
Phase 3 clinical trials, stability studies and manufacturing process validation	1 g caplets with (b) (4) starting (b) (4) at (b) (4) kg scale

The (b) (4) of (b) (4) from (b) (4)% to (b) (4)% (b) (4) Bridging of these formulations is a review issue under the NDA.

The stability data exhibit a (b) (4) This is a review issue under the NDA.

The NDA submission did not include the dissolution method report, nor the analytical validation report for the assay used to evaluate the dissolution samples. These reports will be requested.

### Biopharmaceutics Filing Comments

The following comments have been sent to the Applicant as an information request dated 10/1/13.

1. Submit the dissolution method development report which should include the following:

(b) (4)

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

(b) (4)

2. Your NDA submission only included the dissolution-stability data for the (b) (4) minutes time point. Submit the complete dissolution profile (b) (4) data for the stability registration batches. If you have not collected dissolution profile data at all the time points, please start immediately collecting it for the stability batches and submit it to FDA as soon as it becomes available.
3. The analytical method validation report “METHVAL-0132-R-A-02 Addendum” for the dissolution test mentioned in section 3.2.P.5.3 could not be located. Submit this report or indicate where the report is located in your NDA.

### **RECOMMENDATION:**

ONDQA-Biopharmaceutics has reviewed NDA 205874 for filing purposes and we found this NDA filable from a Biopharmaceutics perspective.

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<b>ONDQA-BIOPHARMACEUTICS</b>				
<b><u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		Section 3.2.P.5 <u>Proposed dissolution method:</u> Apparatus 2 (paddle), 900 mL ethylenediaminetetraacetic acid (EDTA) at 37 °C, at 100 rpm <u>Proposed acceptance criterion:</u> Q = $\frac{(b)}{(4)}\% @ \frac{(b)}{(4)}$ minutes
3.	Does the application contain data to support the proposed dissolution acceptance criteria	x		
4.	Does the application contain the dissolution method development report?		x	The dissolution method development report has been requested.
5.	Does the application contain data on the discriminating ability of the dissolution method		x	The data supporting the discriminating ability of the dissolution method has been requested.
6.	Is there a validation package for the analytical method and dissolution methodology?		x	Section 3.2.P.5.3 refers to: "METHVAL-0132-R-A-02 Addendum" which could not be located. The analytical validation report has been requested.
7.	Does the application include a biowaiver request?		x	Not needed
8.	Does the application include an IVIVC model?		x	Not applicable
9.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not applicable
10.	Is information on mixing the product with foods or liquids included?		x	Not applicable
11.	Is there any <i>in vivo</i> BA or BE information in the submission?		x	The principal pharmacodynamic action of ferric citrate occurs in the GI tract, without systemic absorption. Therefore, the Applicant did not conduct any standard, short-term bioavailability or bioequivalence studies.
12.	Does the application include <i>in vitro</i> alcohol interaction studies?		x	Not needed

## PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
13.	<b>IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?</b>	x		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable
16.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		x	The Biopharmaceutics comments (see comments in pages 2 and 3 of this review) have been sent to the Applicant on 10/1/13 (see information request in DARRTS).

*{See appended electronic signature page}*

Elsbeth Chikhale, Ph.D.  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

10/1/13  
Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

10/1/13  
Date

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/s/  
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ELSBETH G CHIKHALE  
10/01/2013

ANGELICA DORANTES  
10/01/2013