

Pharmacokinetics and Safety of Deferasirox in Subjects with Chronic Kidney Disease Undergoing Haemodialysis

Running title: Deferasirox in chronic kidney disease

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Abstract

Aim: Treatment of chronic kidney disease (CKD) includes parenteral iron therapy, and these infusions can lead to iron overload. Secondary iron overload is typically treated with iron chelators, of which deferasirox is one of the most promising. However, it has not been studied in patients with CKD and iron overload.

Methods: A pilot study was conducted to evaluate the pharmacokinetics and safety of deferasirox in 8 haemodialysis-dependent patients, who were receiving intravenous iron for treatment of anaemia of CKD. Deferasirox was administered at two doses (10 mg/kg and 15 mg/kg), either acute (once daily for two days) or steady-state (once daily for two weeks).

Results: A dose of 10 mg/kg in either protocol was not sufficient to achieve a plasma concentration in the therapeutic range (acute peak 14.1 and steady-state 22.8 $\mu\text{mol/l}$), while 15 mg/kg in either protocol maintained plasma concentration well above this range (acute peak 216 and steady-state 171 $\mu\text{mol/l}$). Plasma concentration observed at 15 mg/kg was well above that expected for this dose (40-50 $\mu\text{mol/l}$), although no adverse clinical events were observed.

Conclusion: This study highlights the need to profile drugs such as deferasirox in specific patient groups, such as those with CKD and iron overload.

Key words: chronic kidney disease, ferritin, iron overload, chelation, deferasirox

Introduction

Iron is an essential element in the body, forming the core of both haemoglobin and myoglobin. A healthy individual will have 4 - 5 g iron in their body, and the 1 - 2 mg lost per day is replenished by absorption from the duodenum. Iron levels are regulated, as iron can cause significant damage to cells through formation of peroxide radicals¹. This can result in life-threatening damage to the heart, liver, brain, pancreas and joints². Iron overload is caused by inherited disorders of metabolism or acquired from exogenous administration (e.g. iron administration or blood transfusion). The latter often occurs in the setting of haematological disorders with ineffective erythropoiesis.

Chronic kidney disease (CKD) is often associated with anaemia, due to deficient production of erythropoietin, and also reduced iron absorption and availability^{3, 4}. This is partly due to increased production of hepcidin, the hormone that regulates iron absorption⁵. The treatment for anaemia consists of both parenteral iron supplements and erythropoiesis stimulating agents (ESA)⁶⁻⁸, although there is evidence of increased morbidity and mortality and many users become resistant to ESA⁹. Multiple infusions of iron are usually administered^{10, 11} and these can result in overload. Whilst serum iron studies, including ferritin levels, have been used to monitor iron toxicity and guide replacement, ferritin can be affected by factors such as inflammation and infection¹. We have recently shown that serum studies are inadequate for guiding iron status in subjects with CKD¹². Furthermore, 60% of haemodialysis subjects have hepatic iron concentration (HIC) greater than twice normal¹³.

Secondary iron overload disorders are usually treated with iron chelation agents. While oral deferiprone¹⁴ is available in Australia for patients with thalassaemia major who are

unable to take desferrioxamine therapy or in whom desferrioxamine therapy has proven ineffective, deferasirox is the first oral iron-chelating drug approved by the Therapeutic Goods Administration for the reduction of chronic iron overload in patients with disorders of erythropoiesis. Although deferiprone has been available for several years, no pharmacokinetic data is available for patients on haemodialysis.

Deferasirox has a high, specific affinity for iron¹⁵, and is effective as a single daily dose. In patients over 16 years old with β -thalassaemia and transfusional iron overload, a dose of 20 mg/kg/day will maintain plasma levels within the therapeutic range of 15-20 $\mu\text{mol/l}$ (trough) to 60-100 $\mu\text{mol/l}$ (peak) over 24 hours¹⁶. Deferasirox is metabolised through hepatic glucuronidation¹⁷, which can vary greatly from patient to patient. In many countries, regulatory authorities have approved the use of deferasirox in patients with creatinine clearance > 40 ml/min, simply because of the lack of safety and pharmacokinetic data. Moreover, the manufacturer's prescribing information warns against the use of deferasirox in patients with impaired renal function due to reported cases of acute renal failure.

There is a pressing need to evaluate efficacy and safety of potential therapies of iron overload complicating CKD. Access to accurate measurements of plasma deferasirox levels is limited^{18, 19}. The aims of this study were to (1) develop and validate a simple method for the analysis of deferasirox in human plasma, and (2) conduct a phase 1 safety study of the administration of deferasirox at 10 mg/kg and 15 mg/kg daily in stable subjects undergoing haemodialysis for CKD, with monitoring of side effects and plasma deferasirox levels.

Methods

Study subjects and protocol

An open label, single arm, phase I pilot study to evaluate the pharmacokinetics and safety of deferasirox at 2 dose levels of 10 mg/kg/day and 15 mg/kg/day was conducted in 8 haemodialysis-dependent patients, who were receiving intravenous iron and erythropoietin therapy for treatment of anaemia of CKD. Power analysis determined that with $n = 4$, we had 90% power to detect a difference of 15 $\mu\text{mol/l}$, where $\alpha = 0.05$ and $\text{SD} = 5$, and 85% power to detect a difference of 35 $\mu\text{mol/l}$, where $\text{SD} = 15$.

Subjects were included if they were able to provide written informed consent, aged 18-80 years, and fulfilled the following criteria: CKD dependent on haemodialysis for at least 2 years; requirement for intravenous iron and erythropoietin therapy as per the current best practice protocol in use at Fremantle Hospital and Health Services; received a minimum of 4 g total intravenous iron in the 2 years before study entry; transferrin saturation $>25\%$; haemoglobin ≥ 110 g/L for the 3 months preceding enrolment; normal or minimally abnormal cardiac function (NYHA Class 1, left ventricular ejection fraction $\geq 50\%$ measured by echocardiography or nuclear medicine); expected life expectancy > 12 months; no significant comorbidity which would preclude deferasirox therapy; pre-menopausal female patients who were sexually active must use an effective method of contraception, or must have undergone clinically documented total hysterectomy, ovariectomy, or tubal ligation and have a negative pregnancy test.

Exclusion criteria included: significant comorbid conditions which in the opinion of the treating nephrologist would preclude inclusion in the study; homozygosity for C282Y mutation or compound heterozygosity for C282Y/H63D mutations in HFE gene; active

gastrointestinal bleeding or other source of blood loss; alanine aminotransferase > 5 x upper limit of normal; patients with uncontrolled systemic hypertension; haemolysis or other haematological disorder which reduces haemoglobin level; past malignancy with potential to influence study outcome; pregnant or breast feeding; patients treated with systemic investigational drugs within the past 4 weeks or topical investigational drugs within the past 7 days; history of non-compliance, or unwilling to comply with the protocol; history of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the run-in period; patients with a known history of HIV; life expectancy of < 12 months.

Four subjects received a daily dose of deferasirox (Exjade) 10 mg/kg administered at 0800 starting on a pre-dialysis day (Day 1) with repeated sampling for pharmacokinetic studies over the next 48 hours covering the rest of the pre-dialysis day and the subsequent dialysis day. Blood was taken at time 0 (pre-dose), 2, 4, 6, 8, 24 (pre-dose), 26, 28, 30, 32 and 48 (pre-dose) hours for each patient. Each patient then received deferasirox 10 mg/kg/day for a further 2 weeks and had pharmacokinetic studies repeated over 48 hours (on Days 15 and 16, at steady-state), starting on a non-dialysis day and continuing over the subsequent dialysis day. During the 2-weeks steady-state study period, erythropoietin and iron were maintained unchanged, and dialysis treatment time for all patients was 270 minutes. The study protocol was then repeated on four different subjects who received a daily dose of deferasirox 15 mg/kg. The baseline characteristics of the study subjects are summarised in Table 1.

Deferasirox assay

LC-MS grade methanol (MeOH) and acetonitrile (ACN) were obtained from Honeywell Burdick and Jackson (Muskegon, USA). Formic acid was obtained from Sigma-Aldrich (St. Louis, USA). Milli-Q water was obtained from an in-lab Milli-Q system (Millipore Corp., Billerica, USA). Plasma samples were collected in sterile glass vials and stored at -80°C.

Deferasirox and $^{13}\text{C}_6$ -deferasirox standards were obtained from Novartis (North Ryde, Australia) and Alsachim (Illkirch-Graffenstaden, France) respectively. Due to low solubility in water, standards were first dissolved in methanol and subsequently diluted into 95% water/5% acetonitrile with 1% formic acid, representing the initial HPLC mobile phase composition. Both labelled and unlabelled standards were analysed over the concentration range 0.1 to 1000 ng/ml.

Sample preparation was adapted from the method of Chauzit *et al.*¹⁹. 100 μl of plasma was combined with 100 μl of internal standard solution and diluted 1:9 with dipotassium phosphate buffer (0.1 M, pH 3). This solution was vortexed for 5 seconds to convert the iron chelate back to free drug. Acetonitrile was added (300 μl) and vortexed for 30 seconds to precipitate proteins. The solution was centrifuged at 13000 g and 20°C for 5 minutes and the supernatant was diluted 1:99 with 95% water/5% acetonitrile with 1% formic acid.

Samples were analysed on a Varian 212-LC with PAL autosampler. The column used was a Restek Ultra Aqueous C_{18} (100 x 2.1 mm, 3 μm). The flow rate was 0.2 ml/min and the mobile phase consisted of: A: H_2O + 1% formic acid; B: acetonitrile + 1%

formic acid. The HPLC gradient was as follows (%A:B): 0 min – 95:5; 3 min – 95:5; 10 min – 0:100; 15 min – 0:100; 17 min – 95:5; 20 min – 95:5.

The HPLC was coupled to a Varian 325-MS triple quadrupole mass spectrometer with a vortex electrospray ionisation source (Agilent Technologies, USA). Drying gas was set at 300°C and 25 psi, nebulizing gas was set at 70 psi and vortex gas was set at 300°C and 30 psi. Capillary voltage was set to 140 V in positive ionisation mode and -84 V in negative mode; and CID gas (argon) pressure was 2 mTorr. Automated MS/MS breakdown was performed on each standard to determine the appropriate transitions for analysis. Six transitions, three in positive ion mode and three in negative, were identified for both labelled and unlabelled forms of the drug. For the unlabelled drug, the following transitions were used: positive m/z 374 \rightarrow 108, 136 and 240; negative m/z 372 \rightarrow 133, 252 and 328. For the labelled drug, the same transitions were used + m/z 6.

The LC-MS/MS method was validated for the following parameters: selectivity, recovery, precision, linearity and sensitivity. Selectivity was determined by analysis of both spiked and drug-free plasma to determine the presence of any co-elution from matrix interference. Recovery was calculated by spiking deferasirox standard into plasma at the commencement and conclusion of sample preparation. Intra-day precision was determined by performing 5 replicate injections of deferasirox standard spiked into plasma (5, 50 and 500 ng/ml) and calculating a relative standard deviation (%RSD). This was performed over three consecutive days to assess inter-day precision. Linearity was determined by plotting a standard curve of peak area versus drug concentration over the 0.1 to 500 ng/ml. Sensitivity was determined as a limit of detection with a signal-to-noise ration not less than 3:1 and a limit of quantification with a ration of not less than 10:1.

Data analysis

LC-MS data was analysed using Varian Workstation v. 7 (Agilent Technologies, USA). Concentration values below the limit of quantification were set at zero. Non-compartmental pharmacokinetic analysis (Kinetica Version 5.0; Thermo Fisher Scientific, Waltham MA, USA) was used to determine the area under the plasma concentration-time curve ($AUC_{0-\infty}$; AUC_{ss}), the area under the first moment-time curve (AUMC), mean residence time (MRT), apparent clearance at steady state ($CL/F = \text{Dose}/AUC$, where F is bioavailability), apparent volume of distribution at steady state ($V_{ss}/F = CL \times MRT$) and the average plasma concentration at steady state ($C_{ss,av}$). The $AUC_{0-\infty}$ was determined for the first (pre-dialysis) and second (post-dialysis; adjusted for residual effects from the first dose) doses on Days 1 and 2 respectively. The AUC_{ss} (AUC within the 24-hour dosing interval at steady-state; equivalent to $AUC_{0-\infty}$) was determined for the pre- and post-dialysis doses on Days 15 and 16 respectively. Peak and trough plasma concentrations were determined from the concentration-time data.

Results

Deferasirox assay

Both deferasirox and $^{13}C_6$ -deferasirox eluted from the column with a retention time of 8.9 minutes. Extraction of drug-free plasma showed no interference on any of the twelve MS/MS transitions used for labelled and unlabelled drug. Extraction recovery of deferasirox was 93%. Standard curves for both forms of the drug were linear over the range analysed ($r^2 = 0.99$ for both). The limit of detection for both forms of the drug was 0.1 ng/ml and the limit of quantification was 0.5 ng/ml. Overall the assay had an

intra-day precision of 6.1% RSD, with the three concentrations having precision as follows: 5 ng/ml: 5.8%; 50 ng/ml: 9.2%; 500 ng/ml: 3.2%. The overall inter-day precision was 5.9% RSD, with the three concentrations as follows: 5 ng/ml: 4.3%; 50 ng/ml: 3.7%; 500 ng/ml: 9.8%.

Patient data

The baseline characteristics of the study subjects are summarised in Table 1, and there were no significant differences observed between the two patient groups for any of the parameters measured. Mean time on dialysis was substantially higher for patients receiving the 10 mg/kg dose (852 ± 128 days) than the 15 mg/kg dose (576 ± 234 days), although this was not statistically significant ($p = 0.8$).

There was no attrition, and all patients completed the full study. During the course of the study, there were no observed adverse clinical or biochemical test parameters on any of the study subjects at deferasirox doses of 10 mg/kg or 15 mg/kg daily (Table 2).

Pharmacokinetic studies of deferasirox

Pharmacokinetic data is summarised in Table 3. For the 10 mg/kg study, both acute and steady-state treatments show the same trend in mean plasma deferasirox concentrations pre- and post-dialysis. For the acute dose, deferasirox peaked at $8.1 (\pm 5.6) \mu\text{mol/l}$ and the trough was $3.2 (\pm 1.7) \mu\text{mol/l}$. Post-dialysis, the peak and trough deferasirox concentrations were $4.1 (\pm 2.5) \mu\text{mol/l}$ and $4.1 (\pm 1.8) \mu\text{mol/l}$ respectively. The $\text{AUC}_{0-\infty}$ for the first dose (pre-dialysis) was $154 (\pm 163) \mu\text{mol.h/l}$ and the $\text{AUC}_{0-\infty}$ for the second dose (post-dialysis; adjusted for residual effects from the first dose) was $239 (\pm 147) \mu\text{mol.h/l}$.

With a steady-state dose of 10 mg/kg/day, deferasirox peaked at $13.8 (\pm 9.2) \mu\text{mol/l}$ and dropped to $5.3 (\pm 2.4) \mu\text{mol/l}$ at 24 h (Figure 1). Post-dialysis, it peaked at $22.8 (\pm 4.5) \mu\text{mol/l}$ and at 48 h had dropped to $7.9 (\pm 3.9) \mu\text{mol/l}$. The pre-dialysis AUC_{ss} , CL/F , $\text{V}_{\text{ss}/\text{F}}$ and $\text{C}_{\text{ss,av}}$ were $207 (\pm 168) \mu\text{mol.h/l}$, $0.21 (\pm 0.15) \text{l/h/kg}$, $2.0 (\pm 1.2) \text{l/kg}$ and $8.6 (\pm 7.0) \mu\text{mol/l}$ respectively. The post-dialysis AUC_{ss} , CL/F , $\text{V}_{\text{ss}/\text{F}}$ and $\text{C}_{\text{ss,av}}$ were $326 (\pm 190) \mu\text{mol.h/l}$, $0.11 (\pm 0.06) \text{l/h/kg}$, $0.9 (\pm 0.4) \text{l/kg}$ and $13.6 (\pm 7.9) \mu\text{mol/l}$ respectively.

For the 15 mg/kg study, both acute and steady-state treatments show the same trend in mean plasma deferasirox concentrations pre- and post-dialysis. For the acute dose, deferasirox peaked at $129.4 (\pm 62.0) \mu\text{mol/l}$ and the trough was $18.7 (\pm 14.0) \mu\text{mol/l}$. Post-dialysis, the peak and trough deferasirox concentrations were $216.2 (\pm 56.2) \mu\text{mol/l}$ and $113.0 (\pm 80.9) \mu\text{mol/l}$ respectively. The $\text{AUC}_{0-\infty}$ for the first dose (pre-dialysis) was $1589 (\pm 1676) \mu\text{mol.h/l}$ and the $\text{AUC}_{0-\infty}$ for the second dose (post-dialysis; adjusted for residual effects from the first dose) was $4814 (\pm 4800) \mu\text{mol.h/l}$.

With a steady-state dose of 15 mg/kg/day, deferasirox peaked at $165.3 (\pm 92.3) \mu\text{mol/l}$ and dropped to $73.1 (\pm 49.5) \mu\text{mol/l}$ at 24 h (Figure 2). Post-dialysis, it peaked at $170.8 (\pm 55.9) \mu\text{mol/l}$ and at 48 h had dropped to $87.6 (\pm 47.0) \mu\text{mol/l}$. The pre-dialysis AUC_{ss} , CL/F , $\text{V}_{\text{ss}/\text{F}}$ and $\text{C}_{\text{ss,av}}$ were $2819 (\pm 3030) \mu\text{mol.h/l}$, $0.03 (\pm 0.02) \text{l/h/kg}$, $0.3 (\pm 0.2) \text{l/kg}$ and $117 (\pm 126) \mu\text{mol/l}$ respectively. The post-dialysis AUC_{ss} , CL/F , $\text{V}_{\text{ss}/\text{F}}$ and $\text{C}_{\text{ss,av}}$ were $2752 (\pm 2388) \mu\text{mol.h/l}$, $0.02 (\pm 0.01) \text{l/h/kg}$, $0.2 (\pm 0.1) \text{l/kg}$ and $115 (\pm 99) \mu\text{mol/l}$ respectively.

Discussion

This study has evaluated the pharmacokinetics and safety of deferasirox in 8 haemodialysis-dependent patients receiving intravenous iron for treatment of anaemia of CKD. It has also presented a new, simple and sensitive assay for deferasirox in plasma samples. Using this method, retention times were stable, justifying the use of 1% formic acid in the mobile phase, rather than a more complicated buffer. By taking advantage of the increased sensitivity of modern LC-MS systems, samples can be diluted prior to analysis, greatly reducing the potential for matrix interference.

Nisbet-Brown *et al.*¹⁶ determined that for gap-free chelation coverage, plasma levels of deferasirox should be maintained between 15-20 (trough) and 60-100 $\mu\text{mol/l}$ (peak), and used a dose of 20 mg/kg to achieve this in adult patients with β -thalassaemia. In this study, a dose of 10 mg/kg was insufficient to reach the suggested therapeutic concentrations with either acute or steady-state doses, although post-dialysis values for the steady-state doses were within this range. Doses of 15 mg/kg (both acute and steady-state) maintained levels within or above this range.

The primary aim of this study was to determine the pharmacokinetics of deferasirox in haemodialysis patients, not to determine its efficacy. Thus, we included patients who did not have a risk for iron overload as indicated by ferritin levels $\geq 1000 \mu\text{g/L}$. With regards to the utility of ferritin in predicting start and stop rules for deferasirox treatment, this is primarily in secondary iron overload settings. We^{12, 20} and others²¹ have recently shown that elevated serum ferritin levels do not accurately predict or correlate with body iron stores in the general population or renal dialysis patients in

particular. Others^{22, 23} have shown similar findings in secondary iron overload patients with low specificity for ferritin in assessing iron overload.

Plasma concentrations observed at a dose of 15 mg/kg, with either protocol, were much higher than previously observed in non-hemodialysis patients. Galanello *et al.*²⁴ observed peak concentrations of 32.3 $\mu\text{mol/l}$ with a single dose of 10 mg/kg and 64.3 $\mu\text{mol/l}$ with a single dose of 20 mg/kg in patients with transfusion-dependent β -thalassemia. In contrast to the 10 mg/kg study, post-dialysis concentrations for the acute dose were higher than for the steady-state dose, which was unexpected. No clear clinical reason for this elevated concentration was observed, although a contributing factor was one patient who had levels approximately 3-fold higher than the other patients (peak 438 $\mu\text{mol/l}$). This highlights the need to evaluate drugs such as deferasirox in specific patient groups in which they are being considered, even when the primary method of drug clearance is not expected to be altered by underlying disease processes, such as those with CKD and iron overload.

There are no data pertaining to the ability of deferasirox to be dialysed, however the compound binds to albumin (40 g/L) at 98-99% efficiency for deferasirox concentrations between 10 and 105 $\mu\text{g/mL}$ ²⁵. Deferasirox and its metabolites are primarily excreted in the faeces (84% of the dose), and renal excretion of deferasirox and its metabolites is minimal (8% of the dose). Thus, it is not anticipated that haemodialysis would significantly affect the clearance of the drug.

Although pharmacokinetic data in patients without CKD would suggest minimal risk of accumulation of deferasirox owing to the minimal urinary excretion, the nearly 10-fold increase in AUC for deferasirox at a dose of 15 mg/kg compared to 10 mg/kg in our

haemodialysis cohort suggests that uraemia may reduce faecal excretion or enhance intestinal reabsorption of deferasirox, thus resulting in higher than predicted plasma levels. In uremic rats, a decrease in intestinal protein membrane transporters such as P-glycoprotein (Pgp) and multidrug-resistance-related protein (MRP2) expression and function secondarily to serum uremic factors has been reported²⁶. This reduction could explain the increased bioavailability of drugs such as deferasirox, which is known to be excreted via MRP2¹⁷, in renal failure. Deferasirox is also known to bind to α 1-acid glycoprotein, but this binding decreases from 85% to 8% as deferasirox concentration increases from 0.5 to 105 μ g/ml²⁵. Pharmacokinetic studies of other drugs that bind to α 1-acid glycoprotein, such as ropivacaine²⁷, have a greater AUC in uraemia, which may also have contributed to the increased bioavailability of deferasirox observed in this study.

This study has highlighted the need to profile drugs such as deferasirox in patients with chronic kidney disease and iron overload. The pharmacokinetics of deferasirox were different than expected in these patients, with a small dose incrementation from 10 to 15 mg/kg leading to a substantial increase in mean plasma concentration. While no adverse clinical parameters were observed in this study, it is clear that further research is needed to avoid potential adverse clinical outcomes and evaluate therapeutic efficacy for iron removal.

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Figure legends

Figure 1: Mean plasma concentration (\pm SD) of deferasirox following steady-state doses of 10 mg/kg. Dialysis occurred at 24 hours. Doses were 10 mg/kg/day for 2 weeks prior to the study, with deferasirox plasma concentrations measured at day 14 and 15.

Figure 2: Mean plasma concentration (\pm SD) of deferasirox following steady-state doses of 15 mg/kg. Dialysis occurred at 24 hours. Doses were 15 mg/kg/day for 2 weeks prior to the study, with deferasirox plasma concentrations measured at day 14 and 15.

Table 1: Baseline characteristics of the haemodialysis patients undergoing acute deferasirox pharmacokinetic studies

Cohort	10 mg/kg	15 mg/kg
N	4	4
Age (yr)	68 ± 9	69 ± 5
Gender (M/F)	3/1	3 /1
Haemoglobin (g/l)	118 ± 5	127 ± 5
Transferrin saturation (%)	34 ± 5	34 ± 8
Ferritin (µg/l)	597 ± 181	553 ± 215
Ferritin range (µg/l)	254 - 1160	261 - 1290
Time on dialysis (d)	852 ± 128	576 ± 234
Cumulative Fe dose (mg)	4400 ± 1101	3400 ± 809
Mean monthly Fe dose (mg)	100 ± 41	150 ± 29
Weekly erythropoietin dose (u/wk)	8750 ± 5344	10500 ± 4992

Table 2: Safety characteristics of the 8 haemodialysis patients undergoing steady-state pharmacokinetic studies with 2 weeks of daily deferasirox

Cohort	Pre-deferasirox	Post-deferasirox	P-value
Haemoglobin (g/l)	122 ± 6	123 ± 11	0.87
Transferrin saturation (%)	53 ± 20	38 ± 14	0.15
Ferritin (µg/l)	628 ± 485	559 ± 392	0.91
Ferritin range (µg/l)	254 – 1290	191 – 1020	N/A
Parenteral Fe dose (mg/mt)	150 ± 54	133 ± 81	0.68
Erythropoietin dose (U/wk)	9330 ± 6020	8330 ± 7090	0.82

Table 3: Non-compartmental pharmacokinetic data for deferasirox following steady-state (ss) doses of 10 and 15 mg/kg. AUC = area under the plasma concentration-time curve. CL/F = apparent clearance at steady state, where F is bioavailability. V_{ss}/F = apparent volume of distribution at steady state. $C_{ss,av}$ = average plasma concentration at steady state

	10 mg/kg		15 mg/kg	
	Pre-dialysis	Post-dialysis	Pre-dialysis	Post-dialysis
AUC _{ss} ($\mu\text{mol}\cdot\text{h}/\text{l}$)	207 \pm 168	326 \pm 190	2819 \pm 3030	2752 \pm 2388
CL/F (l/h/kg)	0.21 \pm 0.15	0.11 \pm 0.06	0.03 \pm 0.02	0.02 \pm 0.01
V_{ss}/F (l/kg)	1.9 \pm 1.2	0.9 \pm 0.4	0.3 \pm 0.2	0.2 \pm 0.1
$C_{ss,av}$ ($\mu\text{mol}/\text{l}$)	8.6 \pm 7.0	13.6 \pm 7.9	117.5 \pm 126.2	114.7 \pm 99.5