Safety and pharmacokinetics of agalsidase alfa in patients with Fabry disease and end-stage renal disease

Gregory M. Pastores¹, Ellen Boyd², Kerry Crandall², Alison Whelan³, Linda Piersall³ and Natalie Barnett¹

¹New York University School of Medicine, New York, NY, ²Fullerton Genetics Center, Asheville, NC and ³St. Louis Children’s Hospital, St. Louis, MO, USA

Abstract

Background. Fabry disease (FD) is caused by an X-linked deficiency in the activity of alpha-galactosidase A and the resultant accumulation of globotriaosylceramide (Gb3) in multiple tissues. Nearly all classically affected males with FD experience kidney dysfunction, with progression to end-stage renal disease (ESRD) in the third decade of life or shortly thereafter.

Methods. Twenty-two FD patients (20 men and 2 women) receiving dialysis or who had a history of kidney transplantation were treated with agalsidase alfa in an open label setting using the same dosing regimen given to patients without ESRD (0.2 mg/kg every other week). Pharmacokinetics (PK) were determined during and following the initial dose, and safety was evaluated during therapy. Change in plasma Gb3 level was used as a surrogate marker of enzyme activity in vivo.

Results. A typical biphasic plasma elimination profile was seen in both dialysis and transplant patients, similar to that observed in 18 non-ESRD FD patients. Calculated PK parameters were similar to the three patient groups. In the male patients, plasma Gb3 level declined by 43% after 6 months (P < 0.001). Infusion reactions were experienced by 8 of 21 (38%) patients, but did not result in any infusions being stopped prematurely. Anti-agalsidase alfa IgG antibodies were detected in 15.8% of males and 0% female patients. No anti-agalsidase alfa IgE antibodies were detected.

Conclusions. The same dosing regimen of agalsidase alfa may be safely administered to FD patients with ESRD as given to those without ESRD.

Keywords: agalsidase alfa; dialysis; Fabry disease; kidney transplant; pharmacokinetics

Introduction

Fabry disease (FD) is a metabolic disorder caused by an X-linked deficiency in the activity of the lysosomal enzyme alpha-galactosidase A (alpha-Gal A) [1]. Over 380 mutations involving the gene coding for alpha-Gal A (Human Gene Mutation Database at the Institute of Medical Genetics, Cardiff, UK. http://www.hgmd.cf.ac.uk/ac/index.php) have been described. FD occurs with an estimated frequency of 1 in 117 000 births [2,3], although a recent study suggests the incidence may be higher (1 in 3100–37 000) [4]. In affected patients, globotriaosylceramide (Gb3) accumulates in several tissues and organs, including the kidney, heart, vascular endothelium and smooth muscle cells, autonomic nervous system, eye and brain, and is thought to be responsible for the clinical problems seen in FD, such as neuropathic pain, cardiomyopathy, renal failure and stroke [5–8].

Kidney disease is nearly universal in classically affected males. In male FD patients, kidney disease can have its onset in adolescence [9,10], with invariable progression to end-stage renal disease (ESRD) between the ages of 35 and 45 years [11,12]. Prior to the introduction of haemodialysis and kidney transplantation, kidney failure was a primary cause of premature death in male patients with FD. Heterozygous females may exhibit all the signs and symptoms of FD, including kidney dysfunction [8,13], but compared with the affected males, their onset is later and disease severity can be more variable [8]. The few studies that have examined the incidence of renal failure in FD suggest that the proportion of heterozygous females (1.2–12%) who progress to ESRD is much smaller when compared with occurrence among affected male cases (30.8%) [7,8,12,14].

Haemodialysis, peritoneal dialysis and kidney transplantation are commonly used to treat ESRD in FD patients [15,16]. Although these procedures address the renal dysfunction of FD, they do not treat the extra-renal aspects of the disease [17]. Enzyme replacement...
therapy (ERT) with bio-engineered human α-Gal A is now available for the treatment of FD [18,19], but reports of its use in FD patients with ESRD are limited to small studies or case reports [20,21]. Thus, this study of ERT in patients with FD on dialysis or with a history of kidney transplantation was performed to examine the safety of agalsidase alfa treatment and to characterize the first-dose pharmacokinetics (PK). The PK study was performed to determine whether any agalsidase alfa dose adjustment would be necessary in adult male and female patients with FD and ESRD.

Subjects and methods

This study was a phase II, multi-centre, open-label trial. Adult male and female patients with FD and ESRD requiring dialysis (either haemodialysis or peritoneal dialysis) or who had a history of kidney transplantation were eligible for inclusion provided that their history of renal failure was consistent only with FD. In males, the diagnosis of FD was confirmed by a plasma α-Gal A level <1.2 nmol/h/ml and in females by mutation analysis. No patient had previously received ERT for FD. A baseline inventory of organ involvement in FD based on medical and surgical histories was tabulated for each patient. The study protocol was approved by the institutional review board or an independent ethics committee at each site; and all patients signed informed consent documents before enrolling in the study.

Agalsidase alfa

Agalsidase alfa (Replagal®, Shire Human Genetic Therapies Inc., Cambridge, MA, USA) is produced in a genetically engineered human cell line and has the same amino acid sequence and a similar glycosylation pattern as the native enzyme [18]. All patients were infused every other week with 0.2 mg/kg agalsidase alfa delivered over ~40 min. The patients who were receiving dialysis had their agalsidase alfa infusions routinely administered at the conclusion of haemodialysis or after the peritoneal dialysate had been drained. Patients who experienced an infusion reaction while receiving treatment were treated symptomatically and could receive prophylactic pre-medication (oral corticosteroids and/or antihistamines) before subsequent infusions.

Safety

Prior to the first infusion, all patients underwent a baseline evaluation that included a physical examination, clinical laboratory tests [including chemistry, haematology, coagulation, urinalysis and 24 h urine chemistry (in renal transplant patients only)] and an electrocardiogram. During the 12-month study, safety was assessed based on the incidence of treatment-emergent adverse events (AEs) and periodic repetition of the tests noted above. In addition, the presence of serum anti-agalsidase alfa antibodies was determined periodically by enzyme-linked immunosorbent assays.

Efficacy

The study was designed primarily to assess the safety of agalsidase alfa, and no formal evaluation of clinical efficacy was conducted. The in vivo activity of agalsidase alfa was confirmed by monitoring Gb3 levels in the plasma of all patients and in urine sediment of kidney-transplant patients. Gb3 was measured by HPLC as previously described [5]. A decline in Gb3 levels was considered to be indicative of substrate clearance and was used as a surrogate marker for efficacy. Estimated glomerular filtration rate (eGFR) was also determined in kidney-transplant patients. These measurements were conducted at baseline, at the end of month 6 of treatment and at the end of month 12 (i.e. after 1 year of agalsidase alfa therapy).

Pharmacokinetics

A PK study was performed over 8 h following the first infusion of agalsidase alfa. Blood samples were taken at 20, 40, 50, 60 and 90 min and at 2, 3, and 8 h after starting the infusion. Serum was analysed for α-Gal A activity using the conversion of 4-methylumbelliferol-α-D-galactopyranoside using an in vitro fluorescence assay [23]. One unit (U) of enzyme activity was defined as the hydrolysis of 1 nmol of substrate per hour at 37°C at a pH of 4.6. The PK analysis was based on serum–enzyme activity and was performed using a non-compartmental model (WinNonlin® Professional Version 4.1, Model 202, Pharsight Corporation, Mountain View, CA, USA). The following PK parameters were calculated: area under the curve extrapolated to infinity (AUC, min·U/ml), maximum serum concentration (Cmax, U/ml), time of Cmax (Tmax, min), terminal elimination half-life (T1/2, min), mean residence time (MRT, min), serum clearance rate (Cl, ml/min), Cl normalized for body weight (ml/min/kg) and apparent volume of distribution at steady state (Vss, l).

Statistical analysis

Because levels of Gb3 in plasma and the urine sediment are not consistently elevated in heterozygous females, results from the two female patients were excluded from the efficacy summaries. However, treatment-emergent AEs occurring in these two female patients were included in the safety summary of AEs. Mean PK parameters were compared between transplant and dialysis patients using Student’s t-test. In addition, mean PK parameters were compared among the transplant patients, the dialysis patients and a cohort of 18 adult male FD patients without ESRD, who had first-dose PK studies performed at the start of previous clinical trials of agalsidase alfa. ANOVA was used for this analysis. Other statistical tests are described in the text. All values are expressed as mean±SEM.

Results

A total of 22 patients enrolled in the study; nine were currently undergoing haemodialysis and 13 had a history of kidney transplantation. One male dialysis patient withdrew from the study after signing informed consent, but prior to receiving his first dose of
agalsidase alfa. Table 1 shows the demographics and baseline disease characteristics of the study population. Of the 22 patients, 20 were males (90.9%), including 13 (59.1%) who had FD-related pathologies involving six or more organ systems. Of the 13 kidney transplant patients, 9 (69%) were being treated for hypertension with the most commonly used medications being beta blockers (n = 7), calcium channel blockers (n = 3), ACE inhibitors (n = 3) and/or angiotensin receptor blockers (n = 2). Hypertension was being treated in seven of nine (78%) ESRD patients with the most commonly used medications being beta blockers (n = 4), calcium channel blockers (n = 3) and ACE inhibitors (n = 4). Antiplatelet agents (aspirin or clopidogrel) were used by 4 of 13 (31%) transplant patients and by eight of nine (89%) ESRD patients.

The study was terminated prematurely by the sponsor when ERT for FD became commercially available in the United States. At that time, patients had been treated for a median of 42 weeks (range 11–65 weeks; except for one patient who had received only a single infusion before experiencing an adverse event and subsequently died; see safety section subsequently). Treatment compliance was excellent. Only one female dialysis patient missed a single scheduled infusion and two other patients received only a partial infusion during one treatment due to a faulty line filter. No infusions were stopped prematurely due to an infusion-related reaction. Three additional patients (two dialysis and one transplant) withdrew from the study prematurely.

Pharmacokinetics

The results from four patients (two dialysis patients and two transplant patients) were excluded from the PK analysis because of technical deviations with blood sampling; specifically, blood was withdrawn through the same catheter being used to infuse the agalsidase alfa, resulting in extremely high serum activity levels being measured during and immediately after the infusion. For the remaining 17 patients, the typical biphasic serum elimination profile was observed. The mean serum clearance profiles for dialysis and transplant patients were similar (Figure 1). In addition, these mean serum clearance profiles were nearly identical to those determined following the initial dose of agalsidase alfa in 18 non-ESRD adult male FD patients who participated in previous clinical trials of agalsidase alfa (Figure 1, unpublished observations, data on file). The calculated PK parameters for all three cohorts are presented in Table 2. No statistically significant differences were observed between the dialysis and the transplant patients for any PK parameter. Likewise, PK parameters measured in dialysis and transplant patients were similar to those measured and calculated for the group of 18 non-ESRD patients with FD.

Table 1. Demographics and baseline FD characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dialysis (n = 9)</th>
<th>Kidney transplant (n = 13)</th>
<th>All patients (n = 22)</th>
<th>Non-ESRD (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.5 ± 3.3 (40–68)</td>
<td>47.1 ± 2.0 (32–59)</td>
<td>48.1 ± 1.8 (32–68)</td>
<td>36.0 ± 1.8 (25–50)</td>
</tr>
<tr>
<td>Male, female</td>
<td>8, 1</td>
<td>12, 1</td>
<td>20, 2</td>
<td>18, 0</td>
</tr>
<tr>
<td>Race [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (11.1%)</td>
<td>0</td>
<td>1 (4.5%)</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>8 (88.9%)</td>
<td>12 (92.3%)</td>
<td>20 (90.9%)</td>
<td>16 (88.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (7.7%)</td>
<td>1 (4.5%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Duration of Fabry diseasea (years)</td>
<td>12.1 ± 3.2 (0.1–28.8)</td>
<td>20.9 ± 3.5 (3.0–40.8)</td>
<td>17.3 ± 2.6 (0.1–40.8)</td>
<td>12.6 ± 3.1b (1–28)</td>
</tr>
<tr>
<td>Extent of organ system involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1–3</td>
<td>1 (11.1%)</td>
<td>1 (7.7%)</td>
<td>2 (9.1%)</td>
<td>5 (27.8%)</td>
</tr>
<tr>
<td>4–6</td>
<td>4 (44.4%)</td>
<td>3 (23.1%)</td>
<td>7 (31.8%)</td>
<td>11 (61.1%)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>4 (44.4%)</td>
<td>9 (69.2%)</td>
<td>13 (59.1%)</td>
<td>2 (11.1%)</td>
</tr>
</tbody>
</table>

Mean ± SE (range)
aFrom time of diagnosis.
bn = 10 for this parameter.

Mean ± SD (range).

Fig. 1. PK, assessed by mean serum enzyme activity, following a first infusion of agalsidase alfa in dialysis, transplant and non-ESRD Fabry patients. PK values for the non-ESRD Fabry patients (filled triangles) values are from 18 male Fabry patients who had PK analysis following their first dose of agalsidase alfa in two previous ReplagalTM clinical trials (data on file). The filled box represents the duration of the infusion of agalsidase alfa.
No significant differences among patient groups were found for any PK parameter (ANOVA).

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>$C_{\text{max}}$ (U/ml)</th>
<th>AUC (min U/ml)</th>
<th>Cl (ml/min kg)</th>
<th>MRT (min)</th>
<th>$T_{1/2}$ (min)</th>
<th>$V_{\text{ss}}$ (% BW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>11</td>
<td>3478 ± 867</td>
<td>221 006 ± 64 191</td>
<td>3.21 ± 1.18</td>
<td>56 ± 9</td>
<td>77 ± 15</td>
<td>17.6 ± 5.9</td>
</tr>
<tr>
<td>Dialysis</td>
<td>6</td>
<td>3887 ± 1896</td>
<td>216 017 ± 98 403</td>
<td>3.40 ± 1.54</td>
<td>54 ± 12</td>
<td>89 ± 31</td>
<td>19.6 ± 12.5</td>
</tr>
<tr>
<td>Non-ESRD</td>
<td>18</td>
<td>3710 ± 855</td>
<td>256 958 ± 63 499</td>
<td>2.52 ± 0.74</td>
<td>64 ± 8</td>
<td>112 ± 25</td>
<td>16.0 ± 4.3</td>
</tr>
</tbody>
</table>

No significant differences among patient groups were found for any PK parameter (ANOVA).

**Metabolic effects**

At baseline, plasma Gb$_3$ levels averaged $4.76 ± 0.47$ nmol/ml (mean ± SE) in the 20 male dialysis and transplant patients. After 27 weeks of agalsidase alfa treatment, plasma Gb$_3$ had declined to $2.73 ± 0.32$ nmol/ml ($n=15$ and $P < 0.001$), which represents a 43% mean decrease. Similar mean decreases were seen in the dialysis cohort ($n=8$; from $5.33 ± 0.66$ to $3.30 ± 0.73$ nmol/ml, $P=0.066$) and the transplant cohort ($n=12$; from $4.38 ± 0.64$ to $2.45 ± 0.31$ nmol/ml, $P=0.007$). The plasma Gb$_3$ in the five patients who received a total of 1 year of agalsidase alfa therapy (through, week 53) was maintained below pre-treatment levels (at $3.40 ± 0.53$ nmol/ml and $P = 0.017$).

Urine sediment Gb$_3$ was normal ($≤33$ nmol/g creatinine) at baseline in 11 of 12 male transplant patients and in the one female transplant patient. In the one male transplant patient with an elevated urine sediment Gb$_3$ level, the level decreased from $117$ nmol/g creatinine at baseline to $46$ nmol/g creatinine (61% reduction) after 27 weeks (the only post-baseline evaluation in this patient). No urine sediment Gb$_3$ levels could be determined for the dialysis-dependent patients.

In the 12 transplant patients, baseline eGFR averaged 64.5 ± 6.0 ml/min/1.73 m$^2$. After 26 weeks of agalsidase alfa therapy, mean eGFR increased slightly to 71.6 ± 8.0 ml/min/1.73 m$^2$ ($n=10$), a change that approached statistical significance in this relatively small cohort of patients ($P = 0.07$).

**Safety**

All the Fabry patients with ESRD ($n=21$) enrolled in the study who received at least one agalsidase alfa infusion were included in the analysis of safety. Agalsidase alfa was generally well tolerated and had a safety profile similar to that established in FD patients without major kidney involvement and on agalsidase alfa [18]. Of these 21 patients, 20 (95.2%) experienced one or more treatment-emergent AEs. The most common reported AEs were symptoms typically observed in patients with FD or in the general population and included neuropathic pain, nasopharyngitis, diarrhoea (each 6 out of 21, 28.6%) and vomiting (5 out of 21, 23.8%). Infusion reactions, which typically involved chills, fever, headache and/or flushing during or shortly after an infusion, were experienced by 8 out of the 21 patients (38.1%) and in all cases were mild-to-moderate in severity. Four patients experienced a single infusion-related event occurring during the infusions of weeks 1, 11, 20 or 25. Two other patients had recurrent events that started early in the study (week 1 or 5), but resolved after 2–6 weeks. Finally, in two patients, infusion reactions were controlled by pre-treatment with antihistamines and corticosteroids and by extending the infusion time from 40 to about 60 min. In these patients, the initial infusion reaction occurred during the infusions of week 17 or 25. No infusions were terminated prematurely due to an infusion reaction. One patient on dialysis died during the study. He developed pneumonia 13 days after receiving his first infusion of agalsidase alfa and was hospitalized and died of an arrhythmia the following day. Neither the pneumonia nor the arrhythmia was considered by the investigator to be related to treatment with agalsidase alfa. Another patient died 25 days after his final dose of agalsidase alfa due to cancer with metastases to the lung. Likewise, this event was not considered to be related to agalsidase alfa.

Anti-agalsidase alfa IgG antibodies were detected in three (15.8%) male patients during the study. No anti-agalsidase alfa IgG antibodies were detected in two female patients, and no anti-agalsidase alfa IgE antibodies were found in any either male or female FD patients during, the course of the study.

**Discussion**

Kidney involvement is a common finding in male FD patients, with evidence of renal dysfunction or proteinuria usually emerging in their teens to mid-to-late 20s and invariably progressing to ESRD in the fourth or fifth decade of life [11]. The present study is the first report of the use of agalsidase alfa in male or female FD patients with ESRD, who were either dialysis-dependent or who had received a kidney transplant. Treatment with agalsidase alfa was well tolerated in this patient population with advanced FD, with no special safety concerns emerging from this study. The enzyme showed the expected metabolic activity as evidenced by the 43% reduction in plasma Gb$_3$, a magnitude of reduction similar to that seen with long-term therapy in FD patients with preserved kidney function when treated with agalsidase alfa [24] or agalsidase beta [25].
The PK of agalsidase alfa was similar among the dialysis and kidney-transplant patients and was likewise similar to PK in adult male FD patients with mild-to-moderate renal involvement (Figure 1, Table 2). This finding was not unexpected, as the kidneys contribute minimally to the plasma clearance of agalsidase alfa. Agalsidase alfa is a glycosylated protein with oligosaccharides containing a substantial number of mannose-6-phosphate (M6P) moieties [26]; it is cleared from the plasma and directed to lysosome by binding to M6P-specific receptors on cell surfaces throughout the body [27]. Thus, the presence or absence of functional kidneys should not affect the PK of agalsidase alfa, a prediction confirmed in this study (Figure 1).

Although dialysis provides partial correction of the renal deficit in FD patients, these individuals continue to suffer from other aspects of the disease. Indeed, the continuing presence of FD-related cardio- and/or cerebro-vascular involvement likely contribute to the higher mortality experienced by FD patients on dialysis compared with those receiving dialysis for ESRD unrelated to FD [12]. In a study of the United States Renal Disease System database, Thadhani et al. [12] showed that the mean 3 year survival for FD patients on dialysis was 63%, which was significantly less than that seen in a matched group of non-diabetic patients initiating dialysis over the same age range (74%, \(P=0.03\)). Thus, ERT in FD patients with ESRD has the potential to improve survival and/or quality of life by addressing extra-renal involvement, as well as symptoms related to the non-renal effects of the disease.

Long-term experience with ERT in FD patients on dialysis is limited to a recent report of nine Italian patients treated with agalsidase beta [20]. In that study, one female and eight male FD patients on either haemodialysis or peritoneal dialysis for ESRD were treated for 2 years with agalsidase beta. Although all male patients reported improvement in FD symptoms, no safety assessment or objective evaluation of the effect of ERT (e.g. change in plasma Gb3 levels) was reported. Left ventricular mass continued to increase during the 2 years of agalsidase beta therapy in the six patients in whom it was measured. Another small study of three adult male FD patients, who had undergone kidney transplantation and who were treated with agalsidase beta for 13–18 months, reported no treatment-related safety concerns [21].

In the present study, infusions of agalsidase alfa in patients undergoing haemodialysis were performed following the completion of dialysis so as not to interfere with the evaluation of PK. It is likely that the enzyme infusion could be done during dialysis without affecting the activity of the enzyme, because a large protein like agalsidase alfa is unlikely to be dialysed. In a study of 10 patients receiving haemodialysis and being treated with agalsidase beta, steady-state plasma concentrations during infusions were similar when the infusions were performed during dialysis or when they were given separately [28].

Renal replacement by kidney transplantation successfully corrects the absence of renal function in patients with FD and improves survival [15,16,29]. It was originally thought that the transplanted kidney might produce sufficient \(\alpha\)-Gal A to serve as a source of enzyme for the entire body [30], but subsequent reports suggested that extra-renal progression of FD continues despite kidney transplantation. Kramer et al. [17] documented extensive cardiac involvement 14 years post-renal transplant in one patient. Thus, administration of ERT should be considered for transplanted patients to treat organ involvement and symptoms related to the extra-renal aspects of FD. In addition, ERT may prevent the deposition of Gb3 in the vascular endothelium of the grafted kidney, a renal biopsy finding which has been occasionally reported [31,32].

The in vivo activity of agalsidase alfa was assessed by changes in plasma Gb3 in the male patients in this study. At week 27, plasma Gb3 had decreased from baseline by 42.5%. The magnitude of this decrease is similar to that reported for agalsidase alfa and agalsidase beta in patients with normal or mild-to-moderate decreases in renal function [24,25]. Although a decrease in plasma Gb3 indicates that the exogenous enzyme is metabolically active, these changes have not yet been shown to correlate with clinical benefit [33].

**Study limitations**

This study had an open-label design, primarily to evaluate safety and first-dose PK of agalsidase alfa in patients with FD and who were on dialysis or have a history of kidney transplantation; consequently, there was no placebo control group. Although this study is the largest reported cohort in a population of FD patients with ESRD, the relatively short duration of follow-up limits the study’s ability to assess any long-term benefits that might result from longer-term administration of ERT in this patient population.

**Conclusions**

The serum elimination profile of agalsidase alfa in patients on dialysis or with a history of kidney transplantation was similar to that seen in adult FD patients with lesser degrees of kidney involvement. The safety profile of agalsidase alfa administration was also similar between the three patient groups. ERT with agalsidase alfa should be considered in FD patients with ESRD on dialysis or a history of kidney transplantation because it has the potential to positively influence the progression of cardiac disease as well as to reduce extra-renal FD-related symptoms.

**Acknowledgements.** This study was sponsored by Shire Human Genetic Therapies Inc., Cambridge, MA, USA. The authors wish to acknowledge the participation of the following investigators who enrolled patients into this trial: Ira Epstein, DO, Dialysis Center, Fort Worth, TX, USA; Y. Howard Lien, MD,
Enzyme replacement therapy in Fabry disease

University of Arizona, Tucson, AZ, USA; John Mulvihill, MD, Oklahoma University Medical Center, Oklahoma City, OK, USA; Raphael Schiffmann, MD, National Institutes of Health, Bethesda, MD, USA; Abel Tello, MD, Medcenter One, Bismark, ND, USA and Jesse Thoené, MD, Medical Center of Louisiana, New Orleans, LA, USA.

Conflict of interest statement. Dr Pastores is the recipient of research grants from Shire. The other authors have no conflict of interest to disclose.

References


Received for publication: 13.12.06
Accepted in revised form: 1.2.07

Downloaded from https://academic.oup.com/ndt/article-abstract/22/7/1920/1842174 on 19 February 2018