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Key Words:	thalassaemia intermedia, IRON OVERLOAD, iron chelation therapy, deferasirox, chelation efficiency

**Deferasirox administration for the treatment of non-transfusional iron overload in patients with thalassaemia intermedia**

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**Suggested running title:** deferasirox in patients with thalassaemia intermedia

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## Summary

Abnormal iron regulation in patients with thalassaemia intermedia may lead to iron overload even in the absence of transfusions. There are limited data on iron chelator use in patients with thalassaemia intermedia and no guidelines exist for the management of iron overload. We present data from 11 patients with thalassaemia intermedia treated with deferasirox (Exjade<sup>®</sup>, 10–20 mg/kg/day) for 24 months. Liver iron concentration and serum ferritin levels significantly decreased over the first 12 months ( $P=0.005$ ) and continued to decrease over the remainder of the study ( $P=0.005$ ). This small-scale study indicates that deferasirox may be suitable for controlling iron levels in patients with thalassaemia intermedia.

**Keywords:** thalassaemia intermedia, iron overload, iron chelation therapy, deferasirox, chelation efficiency

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## Introduction

Many patients diagnosed with thalassaemia intermedia never (or rarely) receive red blood cell (RBC) transfusion therapy to treat the symptoms of anaemia, however, they remain vulnerable to ongoing iron loading and associated clinical sequelae (Taher *et al*, 2006). The mechanism of iron loading is similar to that observed in patients with hereditary haemochromatosis, whereby enhanced erythropoiesis leads to inappropriately low hepcidin levels resulting in increased intestinal iron absorption (Origa *et al*, 2007). Effective iron chelation therapies have been available for many years, yet there are few studies that have evaluated iron chelation in thalassaemia intermedia-specific patient populations (Cossu *et al*, 1981; Olivieri *et al*, 1992; Pippard & Weatherall, 1988; Pootrakul *et al*, 2003). In one small-scale study of paediatric patients with thalassaemia intermedia, subcutaneous infusion of deferoxamine (Desferal®; DFO; Novartis Pharma AG, Basel, Switzerland) resulted in significant increases in urinary iron excretion (Cossu *et al*, 1981). However, the practical limitations and inconvenience of frequent, prolonged subcutaneous infusions of DFO has a negative impact on quality of life and compliance (Cappellini, 2005; Treadwell & Weissman, 2001). Deferasirox (Exjade®; Novartis Pharma AG, Basel, Switzerland) is a once-daily orally administered iron-chelating agent that has been investigated in patients with various transfusion-dependent anaemias (Cappellini *et al*, 2010) including a pilot study of patients with thalassaemia intermedia over 12 months (Voskaridou *et al*, 2010). Here, we have evaluated deferiasirox therapy for up to 24 months in a population of non-transfused patients with thalassaemia intermedia.

## Patients, materials and methods

### Patients

**Adult** male and female patients with thalassaemia intermedia **with variable genotypes** and evidence of iron overload (serum ferritin levels of  $\geq 500$   $\mu\text{g/L}$  and liver iron concentration [LIC] of  $\geq 2$  mg Fe/g dry weight [dw] estimated by quantitative magnetic resonance imaging [MRI]) were included in this single-centre **investigator-initiated trial** conducted at the 'Aghia Sofia' Children's Hospital. All patients were

transfusion-independent although some had received <20 packed RBC transfusions in their lifetime (Table 1). Patients with impaired kidney or liver function (creatinine clearance  $\leq 70$  mL/min, serum creatinine levels greater than the upper limit of normal [ULN], alanine aminotransferase [ALT] levels  $>3 \times$  ULN), or a life expectancy of <2 years were excluded.

### *Study design*

Eleven patients received deferasirox. Patients initially received deferasirox doses of 10 or 20 mg/kg/day. Dose adjustments were permitted at the end of each year of treatment. Therapy was discontinued when patients reached serum ferritin levels <250 ng/mL and LIC <2 mg Fe/g dw. Patients provided written, informed consent before entering the study. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

### *MRI measurements*

All patients were examined at 1.5 Tesla (Signa HDx, GE, Milwaukee, USA) using an FDA-approved multi-echo gradient sequence with electrocardiograph-triggering and breath-holding. For very high iron overload ( $>15$  mg Fe/g dw tissue and equivalently  $T2^* < 1.7$  ms) an additional single-echo, multi-breath sequence was used, covering a range of 8 echo time values between 0.9 and 3.0 ms, allowing accurate and repeatable measurements of  $T2^*$  as low as 0.4 ms (equivalent to 64 mg Fe/g dw tissue). We note that the MRI protocol used is identical to that used by Wood *et al.* (Wood *et al.*, 2005), so that the equation linking  $1/T2^*$  to LIC published in the aforementioned paper could be applied to our relaxation data to obtain LIC values.

### *Efficacy and safety assessments*

Treatment efficacy was assessed according to changes in serum ferritin levels, as well as hepatic and cardiac iron levels estimated by MRI (multi-echo gradient echo sequence and  $T2^*$  measurements, respectively) and left ventricular ejection fraction (LVEF, calculated from fast imaging employing steady state acquisition sequence multi-phase MR images). Safety parameters included assessment of transaminases (ALT and aspartate aminotransferase [AST]), creatinine, creatinine clearance and

cystatin C levels. Biochemical parameters were measured on a monthly basis, whereas MRI sequences were measured yearly.

*Statistical analysis*

The paired Wilcoxon-test was used for testing significant differences and correlations were analysed using the Spearman's rho correlation coefficient. The analyses were conducted on the data set for all patients who completed at least 12 months of treatment. A type I error ( $\alpha$ ) of 0.05 was used to determine statistical significance in all tests.

**Results**

*Patients*

Eleven patients entered the study between June 2006 and July 2008 (Table I). One patient discontinued after 6 months of therapy (patient #6) and was excluded from the analysis. His ferritin levels after 6 months and 24 months were 4740 ng/mL and 4400 ng/mL, respectively. **MRI-estimated LIC after 20 months of observation did not change from baseline (31.8 and 32 mg Fe/g dw tissue, respectively). Reason for discontinuation was non-compliance due to both inability to cope with chronic treatment and mild gastrointestinal disturbances.** One patient completed only 12 months of deferasirox therapy, as he reached low iron levels, while the remaining nine patients continued treatment for a total of 24 months. Deferasirox was initiated at a dose of 10 mg/kg/day in seven patients, with four of them increasing their dose to 20 mg/kg/day after 12 months. Four patients started deferasirox at the dose of 20 mg/kg/day, mainly because of significant iron burden. Dose was escalated from 20 to 25 mg/kg/day in one patient (patient #7) and reduced to 15 mg/kg/day in another patient after achieving low serum ferritin levels (patient #9).

**Table I. Patient characteristics and baseline demographics (n=11)**

Patient #	Gender	Age at baseline MRI (years)	Genotype	HFE allele	Prior RBC units transfused	Prior chelation	Splenectomy	Baseline serum ferritin (µg/L)	Baseline LIC (mgFe/ gr d.w.)	Starting deferasirox dose (mg/kg/day)
1	F	39	IVSI-6/IVSI-110	N/N	0	None	Yes	536	<b>13.4</b>	10
2	M	40	δβ0/IVSI-110	N/N	0	DFO	No	713	<b>2.1</b>	10
3	M	33	IVSI-6/-87	N/C282Y	2	None	Yes	1954	<b>29.7</b>	20
4	F	31	IVSI-1/Hb Crete	N/H63D	2	None	Yes	885	<b>19.7</b>	10
5	M	25	IVSII-1/δβ <sup>Sicilian</sup>	N/H63D	1	DFO	Yes	1044	<b>12.1</b>	10
6*	M	34	IVSII-1/δβ <sup>Corfu</sup>	N/N	1	DFO	Yes	4086	<b>31.8</b>	10
7	M	25	IVSI-1/IVSI-6	N/H63D	2	None	Yes	1362	<b>31.2</b>	20
8	F	24	IVSII-1/δβ <sup>Sicilian</sup>	N/N	3	None	Yes	847	<b>11.6</b>	10
9	F	35	IVSII-1/N ααα/αα	N/N	10	None	Yes	566	<b>10.6</b>	20
10	M	33	IVSI-110/δβ <sup>Macedonian</sup>	N/N	10	DFO	Yes	2044	<b>21.4</b>	20
11	F	30	IVSI-1/δβ <sup>Macedonian</sup>	N/N	20	None	Yes	879	<b>9.6</b>	10

RBC, red blood cell; HFE, hereditary hemochromatosis gene; N, normal; DFO, deferoxamine. ; d.w.; dry weight liver tissue

\*Patient non-compliant with iron chelation therapy.



Efficacy assessments

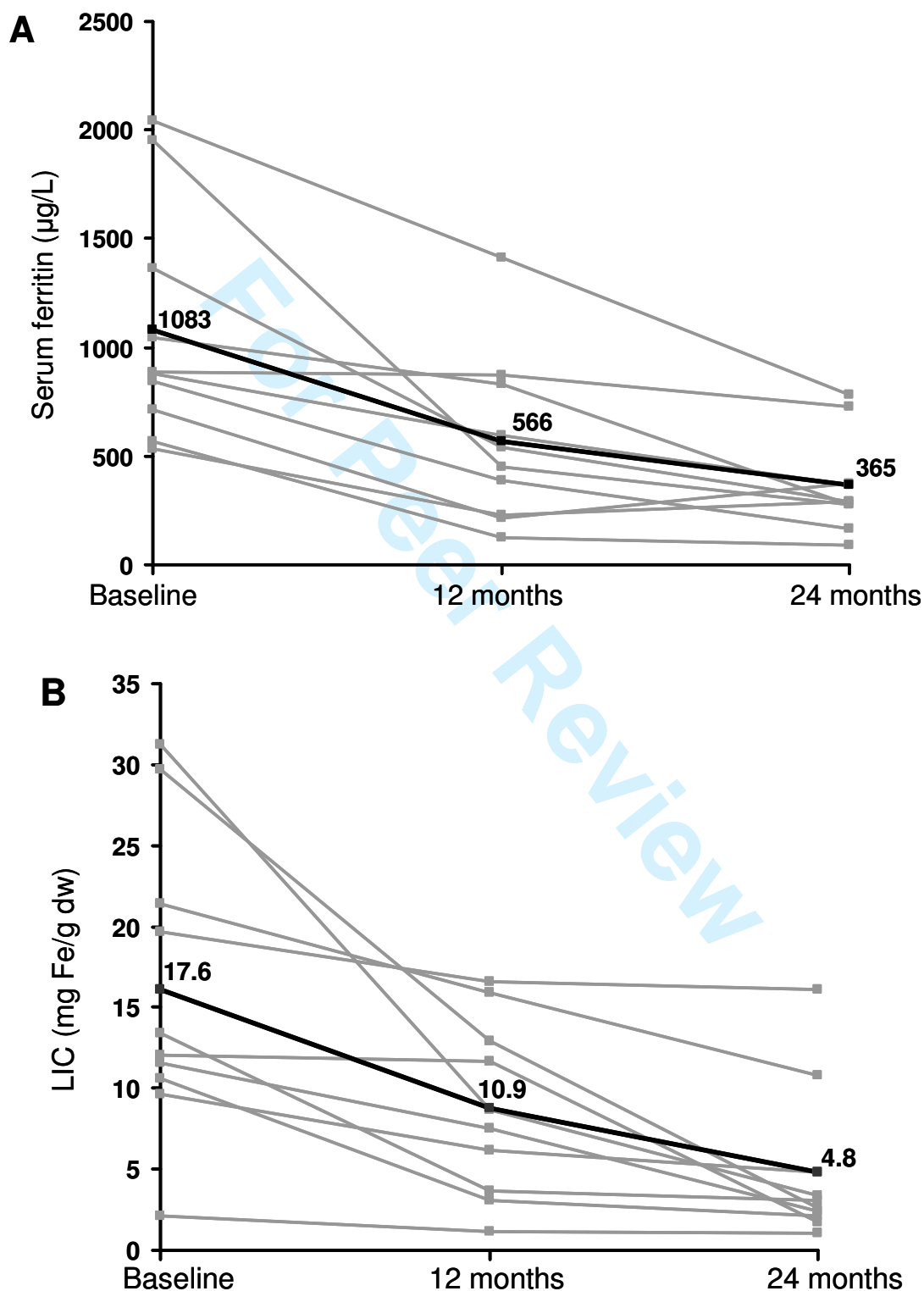
At baseline, serum ferritin levels correlated with LIC ( $r=0.84$ ,  $P<0.005$ ). Serum ferritin levels and LIC decreased significantly over the study period (Fig 1). Mean serum ferritin levels  $\pm$  standard deviation (SD) were reduced from a baseline of  $1083 \pm 538$   $\mu\text{g/L}$  (range 536–2044  $\mu\text{g/L}$ ) to  $566 \pm 389$   $\mu\text{g/L}$  (range 127–1415  $\mu\text{g/L}$ ;  $P=0.005$ ) after 12 months and to  $365 \pm 223$   $\mu\text{g/L}$  (range 93–784  $\mu\text{g/L}$ ;  $P=0.005$ ) after 24 months of deferasirox therapy. Eight patients achieved serum ferritin levels  $<500$   $\mu\text{g/L}$  and six patients achieved levels  $<300$   $\mu\text{g/L}$ . Mean  $\pm$  SD LIC was reduced from  $16.1 \pm 9.2$  mg Fe/g dw (range 2.1–31.8 mg Fe/g dw) to  $8.8 \pm 5.4$  mg Fe/g dw (range 1.2–16.6 mg Fe/g dw;  $P=0.005$ ) after 12 months and to  $4.8 \pm 4.8$  mg Fe/g dw (range 1.1–16.1 mg Fe/g dw;  $P=0.005$ ) after 24 months. Five patients achieved LIC values  $<3$  mg Fe/g dw.

The decrease in LIC was related to deferasirox dose (Pearson’s correlation = 0.45,  $P=0.044$ ), however the dose-dependent rate of hepatic iron removal was slower at low LIC values. If we estimate the total-body iron load based on the formula suggested by Angelucci *et al.* (Angelucci *et al*, 2000) and take into account that deferasirox is a tridentate iron chelator, then the calculated chelation efficiency of deferasirox is variable, between 1 and 38.8% (mean  $17.6 \pm 13.6\%$ ), and seems to decrease at lower LIC values (Fig 2).

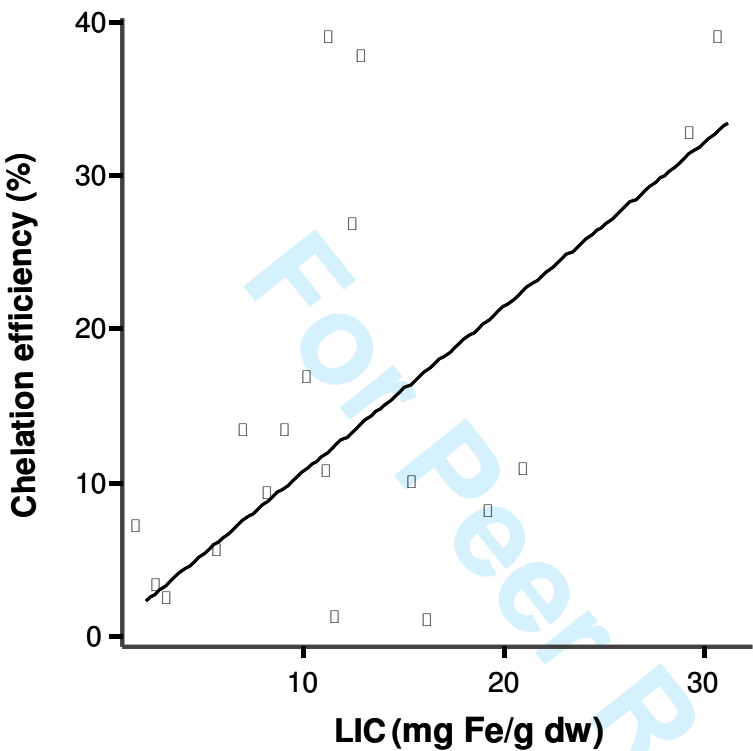
Cardiac T2\* and LVEF levels were within the normal range at baseline, 35.2 ms (range 28.9–37.7 ms) and 66.2% (range 59.6–73.2%), respectively. No changes were seen during the study (T2\* = 35.6 ms and LVEF = 67.6% after 24 months).

The efficacy of treatment was not affected by underlying genotype and/or inheritance of mutations of the *HFE* gene.

**Fig 1.** Change from baseline in A) Serum ferritin levels and B) LIC. Mean values are represented by a single black line, individual patient data by grey lines.



**Fig 2.** Calculated chelation efficiency of deferasirox (Pearsons correlation = 0.45,  $P=0.044$ )



*Safety*

Deferasirox therapy was well tolerated and no serious adverse events were observed. Adverse events were reported in two patients after the first/second weeks of deferasirox administration, including gastrointestinal disorders (mild diarrhoea), dizziness and malaise. Gastrointestinal disorders were resolved by treatment with esomeprazole (Nexium®) and the remainder of adverse events resolved without further intervention or necessity to discontinue/interrupt deferasirox therapy. Creatinine levels did not change during the first year of treatment (mean  $\pm$  SD;  $0.68 \pm 0.13$  mg/dL at baseline vs.  $0.69 \pm 0.12$  mg/dL at 12 months [ $P=0.725$ ]). Elevated levels of creatinine compared to baseline were observed at the end of 24 months of treatment (mean  $\pm$  SD levels at 24 months,  $0.79 \pm 0.18$  mg/dL [ $P=0.005$ ]). Even though changes in creatinine levels seemed to be affected by the rate of LIC changes, this correlation did not reach statistical significance ( $P=0.087$ ). Cystatin C

levels did not change significantly from baseline during treatment (mean  $\pm$  SD;  $0.79 \pm 0.18$  mg/dL at baseline vs.  $0.79 \pm 0.18$  mg/dL at 12 months vs.  $0.80 \pm 0.18$  mg/dL at 24 months [ $P>0.05$ ]). **Similar changes were noted with the creatinine clearance, as estimated by the Cockcroft-Gault formula (mean  $\pm$  SD;  $125.6 \pm 24.5$  ml/min at baseline vs.  $123.7 \pm 26.3$  ml/min at 12 months vs.  $108.5 \pm 20.2$  ml/min at 24 months). Creatinine clearance levels decreased significantly only after 2 years of treatment. None of the patients reached abnormal levels of creatinine clearance or creatinine levels above the ULN.**

A significant decrease in transaminase levels was noted during both the first ( $P=0.005$ ) and second year of treatment ( $P=0.005$ ). Mean  $\pm$  SD ALT levels decreased from  $50.5 \pm 20.4$  U/L at baseline to  $29.9 \pm 14.0$  U/L at 12 months and  $20.0 \pm 9.5$  U/L at 24 months. AST levels decreased from  $42.8 \pm 13.5$  U/L at baseline to  $30.8 \pm 10.7$  U/L at 12 months and  $25.9 \pm 7.2$  U/L at 24 months.

## Discussion

Significant reductions in iron burden as assessed by serum ferritin levels and LIC were achieved with deferasirox therapy over 24 months in this non-transfused population of patients with thalassaemia intermedia, expanding on other previously reported observations over 12 months (Voskaridou *et al*, 2010). The rate of improvement was faster in the first 12 months compared with the later 12 months, suggesting that iron chelation efficiency was more pronounced when iron overload was greater in these patients. Many patients completing 24 months of therapy had reached more acceptable levels of iron burden with serum ferritin levels of  $<500$   $\mu$ g/L and LIC of  $<3$  mg Fe/g dw. Cardiac siderosis was not observed in this patient group and no evidence of cardiac iron accumulation or reduced cardiac function was seen over the course of the study. This observation confirms findings from other institutes (Origa *et al*, 2008; Roghi *et al*, 2009).

Relatively low deferasirox doses of 10–20 mg/kg/day were used in this study and were sufficient to reduce iron burden even in severely iron-overload patients, possibly since patients were receiving **few or no transfusions**. This compares with

higher doses of >30 mg/kg/day required to achieve therapeutic goals in regularly transfused, heavily iron-overloaded patients with  $\beta$ -thalassaemia (Taher *et al*, 2009).

The efficacy of the treatment was not affected by potential genetic factors, which may influence iron accumulation, such as thalassaemia genotype or *HFE*.

Previous studies have suggested a fairly constant chelation efficiency for deferasirox; estimated to be 27% and independent of the dosage used (Porter *et al*, 2005). However, we showed a decrease in the chelation efficiency of deferasirox at lower LIC values. We should underline that the equation for determining chelation efficiency was based on a mathematical formula for estimating total-body iron load derived from studies in regularly transfused ex-thalassaemic patients. Our data may suggest a different behaviour of the chelator in patients with thalassaemia intermedia, who do not generally receive chronic transfusion therapy and therefore may develop different chelatable iron pools compared to patients with thalassaemia major. Nevertheless, these findings suggest that at low LIC values, lower deferasirox doses may be more suitable in order to increase the percentage of chelator that is excreted bound to iron. On the other hand, treatment was well tolerated in this study and did not appear to be associated with significant adverse events, even when levels of low iron load were reached. The improvement in transaminase levels over the course of the study may reflect a decrease in hepatic siderosis as a result of reduced iron burden in the liver, although further analyses are required to confirm this hypothesis. **The observed changes in renal function were within the expected range reported with the use of deferasirox (Cappelini *et al.*, 2010). Creatinine and creatine clearance did not reach abnormal levels in any of the patients. Consequently, close follow up and dosage adjustments are required.**

Baseline iron burden according to LIC and serum ferritin levels in this study population were above threshold levels identified in patients with thalassaemia major to be associated with significant morbidity and mortality (Porter & Davis, 2002). The Thalassaemia International Federation acknowledge the issue of iron overload in patients with thalassaemia intermedia and suggest initiation of iron chelation when

LIC exceeds 7 mg Fe/g dw (Taher *et al*, 2006; Thalassaemia International Federation, 2008). However, effective management guidelines are still required to monitor patients with thalassaemia intermedia for iron overload and provide effective treatment to prevent iron overload-related organ damage.

In conclusion, our results indicate that deferasirox provides effective control of iron levels in rarely or non-transfused patients with thalassaemia intermedia over a 24-month treatment period. **Results need to be verified in randomized placebo-controlled trials. Ongoing, large-scale studies (NCT00873041) will serve to further characterize the utility of deferasirox therapy in this specific patient group, to define appropriate dosages** and help guide the development of effective management strategies for the future.

## Acknowledgements

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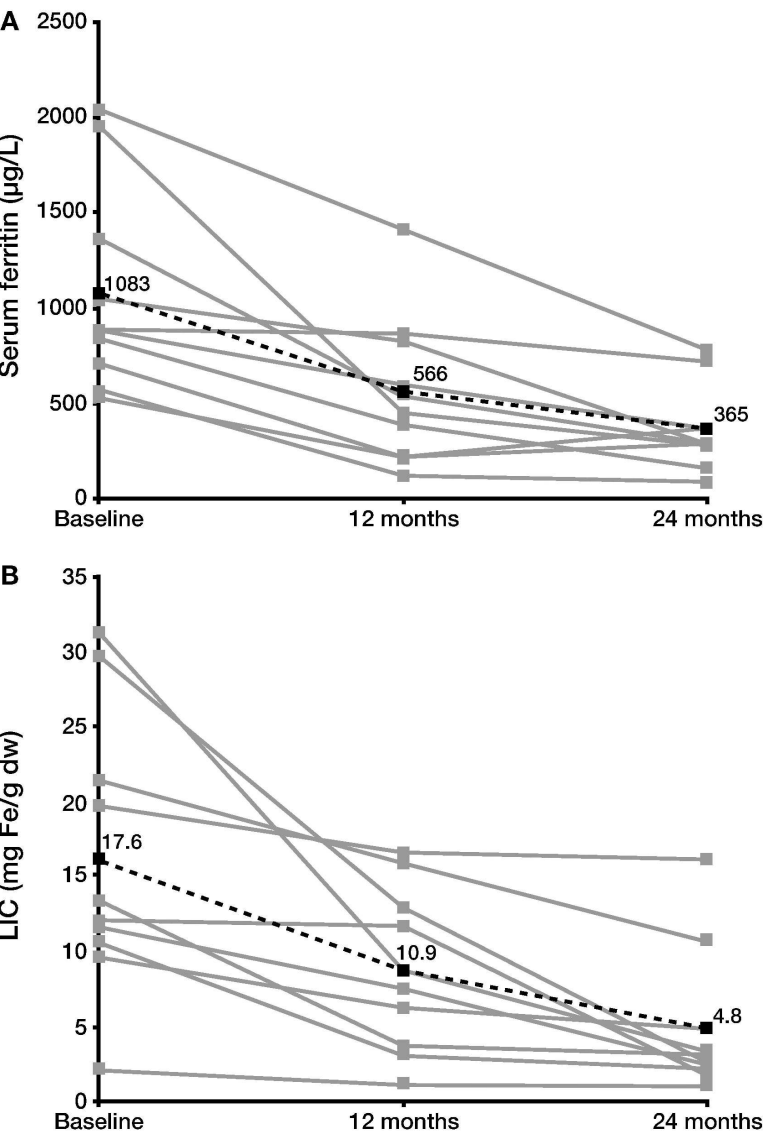
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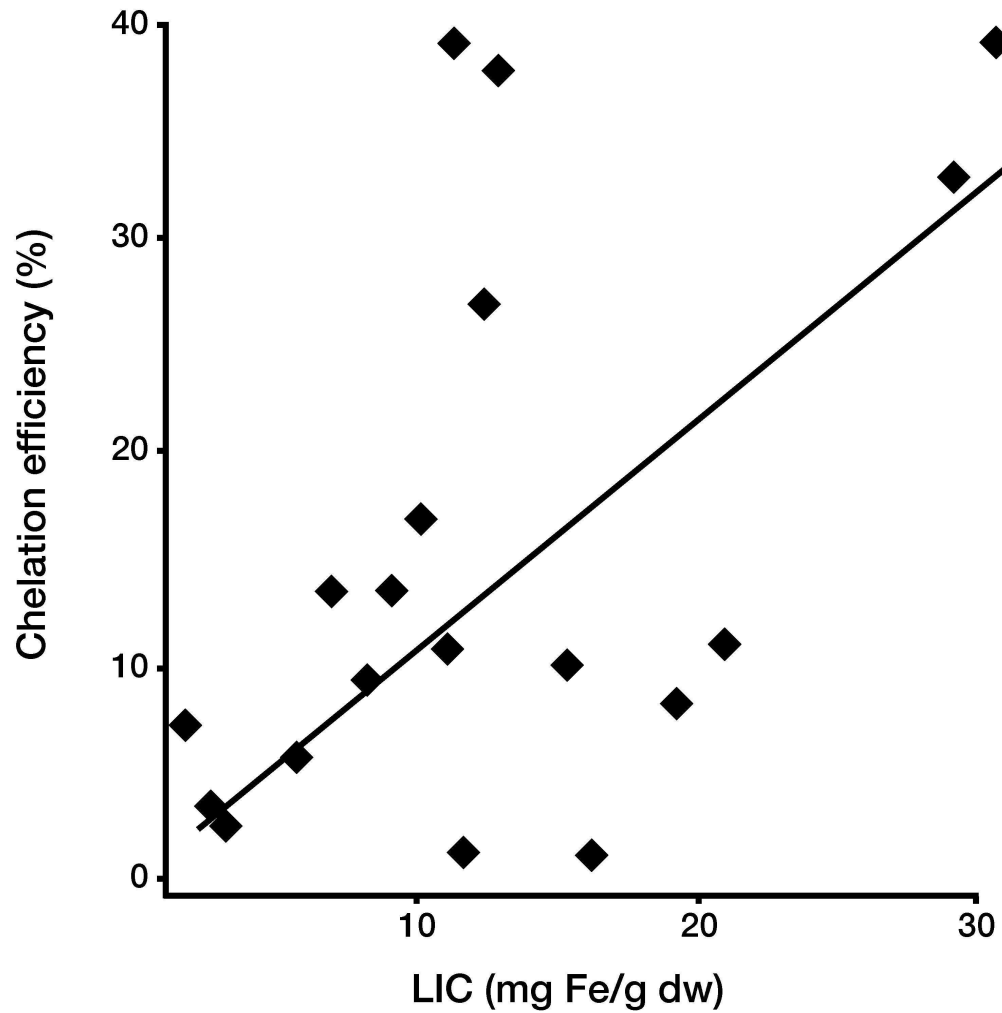
Figure 1



Change from baseline in A) Serum ferritin levels and B) LIC. Mean values are represented by a black dashed line, individual patient data by grey lines.

142x222mm (600 x 600 DPI)

Figure 2



Calculated chelation efficiency of deferasirox (Pearsons correlation = 0.45, P=0.044)  
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