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## **Intravenous iron for the treatment of fatigue in non-anemic, premenopausal women with low serum ferritin concentration**

**Short title:** Intravenous iron for the treatment of fatigue

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**Scientific category:** Clinical Trials and Observations

## ABSTRACT

This is the first study to investigate the efficacy of intravenous iron in treating fatigue in non-anaemic patients with low serum ferritin concentration. In a randomised, double-blinded, placebo-controlled study, 90 premenopausal women presenting with fatigue, serum ferritin  $\leq 50$  ng/mL, and haemoglobin  $\geq 120$  g/L were randomised to receive either 800 mg intravenous iron (III)-hydroxide sucrose or intravenous placebo. Fatigue and serum iron status were assessed at baseline, after 6 and 12 weeks. Median fatigue at baseline was 4.5 (0-10 scale). Fatigue decreased during the initial 6 weeks by 1.1 in the iron group compared with 0.7 in the placebo group ( $p=0.07$ ). Efficacy of iron was bound to depleted iron stores: In patients with baseline serum ferritin  $\leq 15$  ng/mL, fatigue decreased by 1.8 in the iron group compared with 0.4 in the placebo group ( $p=0.005$ ), and 82% of iron-treated vs. 47% of placebo-treated patients reported improved fatigue ( $p=0.03$ ). Drug associated adverse events were observed in 21% of iron-treated patients and 7% of placebo-treated patients ( $p=0.05$ ), none of these events were serious. Intravenous administration of iron improved fatigue in iron-deficient, non-anaemic women with a good safety and tolerability profile. The efficacy of intravenous iron was bound to a serum ferritin concentration  $\leq 15$  ng/mL. This study was registered at the International Standard Randomized Controlled Trial Number Register ([www.isrctn.org](http://www.isrctn.org)) with the number ISRCTN78430425.

**Keywords:** fatigue, iron deficiency, premenopausal women, non- anaemic, intravenous iron, iron sucrose, Brief Fatigue Inventory (BFI), placebo

## **Abbreviations**

BFI, Brief Fatigue Inventory

ITT, intention to treat analysis

SPI, Short Performance Inventory

WHO, World Health Organisation

## INTRODUCTION

Fatigue is a common complaint in general practice, affecting up to one third of the population.<sup>1-5</sup> Similarly, iron deficiency is a frequent disorder affecting about one fourth of menstruating women, as indicated in a French survey which defined iron deficiency by serum ferritin concentrations below 15 ng/mL.<sup>6-8</sup> Women are particularly at risk to develop either or both of these conditions.<sup>9,10</sup>

Different studies have suggested that iron deficiency can cause fatigue symptoms.<sup>11-13</sup> Clinical studies indicate an association between the status of body iron stores and aerobic adaptation during exercise<sup>14-16</sup> as well as cognitive function.<sup>17,18</sup> Recently, Anker et al. showed intravenous iron to improve clinical disease, functional capacity, and quality of life in iron-deficient, non-anaemic patients with chronic heart failure.<sup>14</sup>

Verdon et al. demonstrated that oral iron supplementation improved fatigue in a subgroup of premenopausal non-anaemic women with iron deficiency.<sup>13</sup> Similarly, Beutler et al. showed that women with normal haemoglobin concentration but depleted or reduced bone marrow iron stores experienced improvements in fatigue following oral iron therapy.<sup>11</sup> However, oral iron administration has limitations. It is often accompanied by gastrointestinal side effects and only about 10% of orally administered iron is absorbed by the body.<sup>6</sup>

Investigation of any therapeutic approach to reduce fatigue can be influenced by a strong placebo effect,<sup>19</sup> making a placebo-controlled and blinded study design essential to draw conclusions for medical practice. Prior studies analysing the effect of iron supplementation on fatigue improvement were performed with oral iron, which

can result in an unintended unblinding of patients due to intestinal side effects and stool colouring and thus influence study results.

This is the first study to investigate the efficacy of intravenous iron in the treatment of fatigue in non-anaemic patients (women) with low serum ferritin concentration.

## **PATIENTS AND METHODS**

The FERRIM trial was conducted at four study centres in Switzerland (Policlinic of Internal Medicine, University Hospital of Basel; Division of Internal, University Hospital of Zurich; Gynaekologie & Geburtshilfe in Seefeld, Zurich; Ambulatorium Wiesendamm, Basel) in accordance with the Declaration of Helsinki and the Guidelines on Good Clinical Practice. The protocol and all amendments were approved by the local Ethics Committees at the centres. All patients included in the study gave written informed consent. This study was registered at the International Clinical Trials Registry Platform with the number ISRCTN78430425.

### **Inclusion and exclusion criteria**

Premenopausal, menstruating women  $\geq 18$  years of age who presented with fatigue were evaluated for inclusion in the study. Inclusion criteria were serum ferritin concentration  $\leq 50$  ng/mL, haemoglobin concentration  $\geq 120$  g/L, and adequate contraception for the study period. Exclusion criteria were pregnancy, intake of gestagens repressing menstruation, physical or mental disorders, medication affecting physical or mental performance, iron treatment in the 4 weeks prior to enrolment, and history of hypersensitivity to any iron medication. Patients were withdrawn from the study if serum ferritin concentration exceeded 800 ng/mL or if transferrin saturation exceeded 50% during the study period.<sup>20</sup>

### **Study design**

The FERRIM trial was a randomised, double-blinded, placebo-controlled study. Patients were randomised to receive either a cumulative intravenous dose of 800 mg iron as iron(III)-hydroxide sucrose or intravenous placebo during 2 weeks. The

primary study objective was to determine the efficacy of iron compared to placebo in decreasing fatigue 6 weeks after treatment initiation. Secondary objectives were to determine the impact of iron supplementation on serum ferritin and haemoglobin concentration and to confirm the safety of intravenous iron sucrose. Patients were followed-up for 12 weeks. Subgroups of the study population were analysed to investigate the influence of the serum iron status at baseline on the efficacy of iron treatment.

### **Randomisation and blinding**

The randomisation schedule was generated by Cardinal Health Germany GmbH (Schorndorf, Germany). In total, 172 randomisation numbers were generated.

The control group received placebo (0.9% saline). It was made sure through organisational measures that neither the patient nor the investigator could become aware of whether the active group (dark brown solution) or placebo (colourless solution) was administered. The study medication was prepared and administered by a staff member other than the investigator. Both the infusion bag and the injection site were covered, and non-transparent tubing was used, ensuring that the patient could not see the infusion solution at any time. The investigator was not present during the infusion.

### **Study medication**

Treatment was delivered on 4 days during the first two weeks of the study by a physician assistant who injected either 4 infusions containing 200 mg iron as iron(III)-hydroxide sucrose (Venofer<sup>®</sup>, Vifor Pharma, Switzerland) in 200 mL 0.9% saline or 4 infusions of 200 mL 0.9% saline over a minimum period of 10 minutes

each. The physician assistant took all necessary precautions to ensure that the patient could not see, nor draw any conclusion as to the nature of the solution administered. The work of the physician assistant was done completely independently of the study physicians.

### **Fatigue scores**

Fatigue was assessed at baseline, and after 6 and 12 weeks using the *Brief Fatigue Inventory* questionnaire (BFI).<sup>21,22</sup> Patients were asked to rate the severity of fatigue on a scale from 0 (no fatigue) to 10 (maximum imaginable fatigue) answering standardised questions. Three questions addressed the level of fatigue at its worst, its usual, and current level during the last 24 hours; six questions were aimed at gauging the interference of fatigue with aspects of daily life, including general activity, mood, walking ability, work/housework, relations with other people, and enjoyment of life. According to the original publication validating the BFI, total fatigue score was obtained by calculating the mean of the resulting scores for these questions.<sup>21,22</sup>

Additionally, change in fatigue was assessed 6 and 12 weeks after treatment initiation by the *Short Performance Inventory* questionnaire (SPI). Patients were asked to categorise their current level of fatigue compared with the situation at baseline as improved (slightly better, much better, or completely resolved) or not improved.

### **Laboratory parameters**

The concentrations of haemoglobin, iron, serum ferritin, transferrin, and C-reactive protein were measured at baseline and after 6 and 12 weeks. Patients' levels of

creatinine, alanine aminotransferase, aspartate aminotransferase, and thyroid-stimulating hormone were determined at baseline. Analyses were done in a central laboratory (Rothen Medizinische Laboratorien, Basel, Switzerland).

### **Adverse events**

Adverse events were reported by the patients or assessed by the study physicians at each visit. Adverse events were classified as “serious” or “not serious” and as “drug-associated” or “not drug-associated”. All patients who received at least one dose of study medication were included in the analysis.

### **Statistical analysis**

Results with parametric distribution are presented as mean values ( $\pm$  1 standard deviation), results with non-parametric distribution as median values (quartiles Q1, Q3). Comparisons between the study groups were performed by t-test, Mann Whitney U-test, or  $\chi^2$ -test. Correlations were tested according to Pearson. Intention to treat analysis (ITT) was done including (a) all patients randomised and (b) the patients treated at least once and with at least one post-baseline evaluation in line with the study protocol. Missing values were imputed according to the baseline observation and the last observation carried forward principle.<sup>23</sup> All tests were performed double-sided with a significance level of 5% (0.05).

## RESULTS

### Study population and baseline characteristics

Of 116 premenopausal women presenting with fatigue, 90 were included in the study. Median fatigue score of the study population was 4.5 at baseline as assessed on a scale from 0 to 10 using the BFI questionnaire. Thus, the majority of study patients presented with fatigue levels previously defined as “low” or “moderate”.<sup>21,22</sup> Of the 90 patients, 43 (48%) were randomised to receive intravenous iron (4x200 mg iron as iron(III)-hydroxide sucrose) and 47 (52%) to receive intravenous placebo (4x200 mL 0.9% saline). Forty-two iron treated patients and 44 placebo treated patients underwent post-baseline evaluation (Figure 1).

At baseline, there was no significant difference between the iron and the placebo group with regard to fatigue (4.0 vs. 4.7,  $p>0.10$ ), serum ferritin concentration (24 vs. 20 ng/mL,  $p>0.10$ ), or transferrin saturation (20 vs. 25%,  $p>0.10$ ). The study groups were also well randomised in age, height, body weight, blood pressure, heart rate, and laboratory parameters (Figure 2, Table 1).

### Change in fatigue after 6 weeks

Fatigue decreased in both study groups during the first 6 weeks after treatment initiation as assessed by the BFI score (Figure 2). After 6 weeks, median fatigue decreased by 1.1 in the iron group and by 0.7 in the placebo group ( $p=0.07$ ; Table 2).

Improvement in fatigue 6 weeks after treatment start, as evaluated by the SPI, was reported by 65% of iron-treated and 40% of placebo-treated patients ( $p=0.02$ , Table 2). The most prominent difference between the two study groups was observed in those patients who judged their fatigue to be “much better” after 6 weeks of

treatment. These patients comprised 28% of the iron group but only 13% of the placebo group (Table 2).

### **Change in iron status after 6 weeks**

In iron-treated compared to placebo-treated patients, a significant increase in serum ferritin concentration (98 ng/mL vs. 1 ng/mL;  $p < 0.001$ ) and transferrin saturation (9% vs. 2%;  $p = 0.006$ ) was observed during the 6 weeks following treatment initiation (Table 2). In contrast, haemoglobin levels remained normal and constant in both study groups during this period. As inflammation marker, C-reactive protein remained stable in both groups throughout the study period.

### **Subgroup analyses**

The World Health Organisation (WHO) has defined a cut-off serum ferritin concentration of 15 ng/mL to identify iron deficiency.<sup>24</sup> Therefore, in an additional analysis, the WHO criterion was applied to the present study: efficacy of iron was evaluated in the subgroups of patients with serum ferritin concentration  $\leq 15$  ng/mL ( $n = 34$ ) and  $> 15$  ng/mL ( $n = 56$ ) at baseline. Further analysis was performed in patients with transferrin saturation  $\leq 20\%$  and  $> 20\%$  at baseline.

Among patients with a baseline serum ferritin concentration  $\leq 15$  ng/mL ( $n = 34$ ), median fatigue according to the BFI score decreased by 1.8 in the iron group compared with 0.4 in the placebo group ( $p = 0.005$ ; Table 3 and Figure 3). And improvement in fatigue, as assessed by the SPI, was reported by 82% of iron-treated patients compared with 47% of placebo-treated patients ( $p = 0.03$ ; Table 3). No significant differences between the study groups in BFI or SPI score at 6 weeks were observed in patients with baseline serum ferritin  $> 15$  ng/mL (Table 3).

Similarly, in patients with transferrin saturation  $\leq 20\%$  at baseline, administration of iron resulted in a significantly greater reduction in fatigue than administration of placebo (BFI,  $p=0.01$ ; SPI,  $p=0.002$ ). However, patients with transferrin saturation  $>20\%$  experienced no significant reduction in fatigue (both questionnaires  $p>0.10$ ).

### **Follow-up after 12 weeks**

The decrease in fatigue (BFI) between baseline and 12 weeks was 1.3 in the iron group and 0.9 in the placebo group ( $p>0.1$ ), and improvement in fatigue (SPI) was reported by 63% of iron-treated patients and by 34% of placebo-treated patients ( $p=0.006$ ). Improvements in serum ferritin concentration and transferrin saturation in iron treated compared to placebo treated patients remained significant after 12 weeks ( $p<0.001$  and  $p=0.006$ , respectively; Table 4).

Among patients with a baseline serum ferritin concentration  $\leq 15$  ng/mL, the median decrease in fatigue score between baseline and 12 weeks was 2.3 and 0.7 in the iron and the placebo groups, respectively ( $p=0.03$ ). Improvement in fatigue was reported by 82% of iron-treated patients and by 35% of placebo-treated patients ( $p=0.005$ ; Table 4).

### **Adverse events**

Evaluation of adverse events was performed throughout the study period and included 89 patients who each received at least one dose of study medication. The study groups did not differ significantly in the number of patients reporting adverse events or in the number of adverse events per patient (Table 5). One serious adverse event was observed in the iron group (appendicitis) and one in the placebo group (traffic accident). Neither was classified as drug-associated.

Seventeen drug-associated adverse events were reported among 9 patients treated with intravenous iron while 4 drug-associated adverse events were reported among 3 placebo-treated patients (Table 5). The difference between the study groups was significant regarding the number of patients reporting drug-associated adverse events ( $p=0.05$ ). However, none of these drug-associated events were considered serious – the most frequently observed were nausea, chills, and headache (Table 5). The occurrence of these drug-associated adverse events was limited to the period of drug administration.

## DISCUSSION

This randomised, double-blinded, placebo-controlled study investigated for the first time efficacy and safety of an intravenous iron therapy in the treatment of fatigue in premenopausal non-anaemic women (haemoglobin  $\geq 120$  g/L) with low serum ferritin concentration ( $\leq 50$  ng/mL). A significant effect of iron (compared to placebo) on fatigue was observed exclusively in patients with substantially depleted iron stores – as indicated by a serum ferritin concentration  $\leq 15$  ng/mL at baseline. More than 80% of these patients reported improved fatigue 6 and 12 weeks after treatment initiation, as well as decreases in the severity of fatigue to less than half of the initial value at study completion. These are the first results providing evidence that intravenous supplementation of iron can improve fatigue symptoms in iron deficient, non-anaemic premenopausal women.

In this study, serum ferritin concentration  $\leq 15$  ng/mL or transferrin saturation  $\leq 20\%$  (with serum ferritin concentration  $\leq 50$  ng/mL) were predictive for a significant benefit from intravenous iron therapy. Of these criteria, serum ferritin concentration  $\leq 15$  ng/mL is probably more suitable for use in general practice. However, the size of the study population does not allow definitive determination of a cut-off serum ferritin concentration below which patients benefit from iron therapy.

A total dose of 800 mg intravenous iron administered over two weeks resulted in a marked increase in serum ferritin concentration (98 ng/mL), which indicated sufficient replenishment of body iron stores. Iron administration, however, did not influence haemoglobin concentration, which was in the normal range at baseline and remained constant during the observation period in both iron-treated and placebo-treated patients. Thus, the fatigue-reducing effects of iron therapy reflect the non-

haematological functions of iron. Iron is an essential component of a large number of human metabolic enzymes such as ribonucleotide reductase, NADH dehydrogenase, succinate dehydrogenase, and cytochrome c reductase/oxidase. These enzymes catalyse essential biochemical reactions, e.g., the formation of deoxyribonucleotides and aerobic oxidation of carbohydrates and fatty acids in the mitochondrial citric acid cycle of the respiratory chain.<sup>25-27</sup>

The results of this study are in line with previous studies indicating a beneficial effect of oral iron therapy in comparable patient groups.<sup>11-13,18</sup> Oral iron treatment, however, can be accompanied by gastrointestinal side effects and usually requires administration over several months since intestinal iron absorption is low;<sup>6</sup> both of these factors affect patients' adherence to therapy. In contrast, intravenous iron can efficaciously replenish iron stores with a good safety and tolerability profile.<sup>14</sup> In this study, drug-associated adverse events were observed more frequently in iron-treated (21%) than placebo-treated (7%) patients. However, these events (mainly nausea, chills, and headache) were not serious and occurrence was limited to the period of administration.

Improvement in fatigue after 6 weeks was reported by 40% of placebo-treated patients. Further evaluation of this strong placebo effect showed a significant correlation between baseline fatigue and decrease in fatigue ( $r=0.38$ ,  $p=0.009$ ): patients with high initial fatigue showed a strong response to placebo. This highlights the importance of the emotional component of fatigue in patients who considered themselves to be severely fatigued.<sup>21,22</sup> This observation may be accurate for the present, besides iron-deficient otherwise healthy study population

but not necessarily for other populations, such as patients suffering from fatigue as a result of cancer.

Of note, it is always recommended to carefully search for somatic, psychological and/or social causes of fatigue. Even if a low serum ferritin value is found, a serious cause of iron deficiency, such as gastrointestinal bleeding, malabsorption syndrome, or gynecological diseases must be considered even in premenopausal women.

### **Conclusion**

Intravenous administration of 800 mg iron improved fatigue in iron deficient, non-anaemic women with a good safety and tolerability profile. Response to iron was bound to the degree of depletion of iron stores – as indicated by a serum ferritin concentration  $\leq 15$  ng/mL before treatment. Investigation in a larger population is needed to confirm the condition under which patients benefit from iron therapy.

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## **Author contributions**

PAK, EB, CB, JF and GS planned and initiated the study. PAK and CB recruited the patients. PAK, EB and GS analyzed the data. PAK and GS wrote the manuscript. All authors provided critical revision of the manuscript.

## **Disclosure**

This study was funded by Vifor Pharma, Switzerland. The sponsor of the study was involved in the trial design and was responsible for data collection and storage. The authors had full access to all the data and were responsible for the analysis and interpretation of the data presented in this publication.

Christian Breymann is consulting expert for Vifor Int in the field of Obstetrics and Gynecology. All other authors declare no competing financial interests.

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**Table 1.** Baseline characteristics

	Iron group	Placebo group	p-value
Age, years	31±8	32±7	ns
Height, cm	166±6	166±6	ns
Body weight, kg	60±8	59±7	ns
Blood pressure syst., mm Hg	117±13	117±13	ns
Blood pressure diast., mm Hg	73±8	72±10	ns
Heart rate, 1/min	72±10	71±9	ns
Haemoglobin, g/L	133±6	133±7	ns
Mean red blood cell volume, fl	90±5	90±5	ns
Serum ferritin concentration, ng/mL	24 (10, 32)	20 (14, 28)	ns
Transferrin saturation, (%)	20 (14, 30)	25 (16, 32)	ns
Creatinine, µmol/L	77 (72, 82)	78 (72, 84)	ns
Alanine aminotransferase, U/L	17 (13, 21)	17 (15, 23)	ns
Aspartate aminotransferase, U/L	20 (17, 26)	21 (18, 24)	ns
Thyroid-stimulating hormone, mU/L	1.5 (1.0, 2.0)	1.4 (0.8, 2.0)	ns
C-reactive protein, mg/L	1.1 (1.1, 1.1)	1.1 (1.1, 1.1)	ns

Results are presented as mean values ( $\pm$  1 standard deviation) or median values (quartiles Q1,Q3). p-values were calculated by t-test or Mann Whitney U-test. ns: not significant and no trend ( $p>0.10$ ).

**Table 2.** Change of fatigue and laboratory parameters 6 weeks after treatment initiation with intravenous iron or intravenous placebo

6 weeks after treatment initiation compared to baseline	Iron group	Placebo group	p-value
<b>Change in fatigue (BFI*)</b>			
n=90, ITT all patients randomised	-1.1 (-2.2, -0.3)	-0.7 (-1.3, 0.0)	0.07
n=86, ITT according to protocol <sup>†</sup>	-1.1 (-2.2, -0.4)	-0.8 (-1.4, 0.0)	0.08
<b>Fatigue improved (SPI*), n (%)</b>	28/43 (65%)	19/47 (40%)	0.02
- Fatigue slightly better	12 (28%)	9 (19%)	
- Fatigue much better	12 (28%)	6 (13%)	
- Fatigue completely resolved	4 (9%)	4 (8%)	
<b>Change in laboratory parameters</b>			
Serum ferritin concentration, ng/mL	98 (74, 113)	1 (-7, 5)	<0.001
Transferrin saturation, %	9 (0, 23)	2 (-5, 9)	0.006
Haemoglobin, g/L	1±7	0±6	ns
C-reactive protein, mg/L	0 (0, 0)	0 (0, 0)	ns

Results are presented as mean values ( $\pm$  1 standard deviation), median values (quartiles Q1,Q3), or number of patients (%). p-values were calculated Mann Whitney U-test, t-test or  $\chi^2$  test, ns: not significant and no trend ( $p>0.10$ ).

\* *Brief Fatigue Inventory*: Self reported fatigue on a numeric scale from 0 (no fatigue) to 10 (maximum imaginable fatigue).

<sup>†</sup> Analysis included all patients treated at least once and with at least one post-baseline evaluation.

<sup>†</sup> *Short Performance Inventory*: Self reported categorisation of current level of fatigue compared to baseline as improved (“slightly better”, “much better”, or “completely resolved”) or not improved.

**Table 3.** Change in fatigue 6 weeks after treatment initiation with intravenous iron or intravenous placebo in dependence of the serum ferritin concentration at baseline

<b>6 weeks</b> after treatment initiation compared to baseline	<b>Iron group</b>	<b>Placebo group</b>	p-value
<b>Baseline ferritin ≤15 ng/mL (n=34)</b>			
Change of fatigue (BFI*), median	-1.8 (-2.5,-0.8)	-0.4 (-1.2, 0.0)	0.005
Fatigue improved (SPI <sup>+</sup> ), n (%)	14/17 (82%)	8/17 (47%)	0.03
<b>Baseline ferritin &gt;15 ng/mL (n=56)</b>			
Change of fatigue (BFI*), median	-0.7 (-1.8, 0.0)	-0.8 (-1.4, 0.0)	ns
Fatigue improved (SPI <sup>+</sup> ), n (%)	14/26 (54%)	11/30 (37%)	ns

Results are presented as median values (quartiles Q1,Q3) or number of patients (%). p-values were calculated by Mann Whitney U-test or  $\chi^2$  test, ns: not significant and no trend (p>0.10).

\* *Brief Fatigue Inventory*: Self reported fatigue on a numeric scale ranging from 0 (no fatigue) to 10 (maximum imaginable fatigue).

+ *Short Performance Inventory*: Self reported categorisation of current level of fatigue compared to baseline as improved or not improved.

**Table 4.** Change in fatigue and serum iron status 12 weeks after treatment initiation with intravenous iron or intravenous placebo

<b>12 weeks</b> after treatment initiation compared to baseline	<b>Iron group</b>	<b>Placebo group</b>	<b>p-value</b>
<b>Total study population (n=90)</b>			
Change of fatigue (BFI*), median	-1.3 (-2.4, -0.5)	-0.9 (-2.2, 0.0)	ns
Fatigue improved (SPI <sup>+</sup> ), n (%)	27/43 (63%)	16/47 (34%)	0.006
Change of ferritin concentration, ng/mL	81 (49, 100)	-1 (-7, 4)	<0.001
Change of transferrin saturation, %	7 (0, 17)	1 (5, 6)	0.006
<b>Baseline ferritin ≤15 ng/mL (n=34)</b>			
Change of fatigue (BFI*), median	-2.3 (-3.2, 0.9)	-0.7 (-1.3, 0.1)	0.03
Fatigue improved (SPI <sup>+</sup> ), n (%)	14/17 (82%)	6/17 (35%)	0.005

Results are presented as median values (quartiles Q1,Q3) or number of patients (%). p-values were calculated by Mann Whitney U-test or  $\chi^2$  test, ns: not significant and no trend (p>0.10).

\* *Brief Fatigue Inventory*: Self reported fatigue on a numeric scale ranging from 0 (no fatigue) to 10 (maximum imaginable fatigue).

+ *Short Performance Inventory*: Self reported categorisation of current level of fatigue compared to baseline as improved or not improved.

**Table 5.** Adverse events

	Iron group	Placebo group	p-value
<b>All adverse events</b>			
Number of patients reporting events, n	23 (53%)	31 (66%)	ns
Total number of adverse events, n	52	53	ns
Number of serious adverse events, n	1	1	
- appendicitis	1	0	
- traffic accident	0	1	
<b>Drug associated adverse events</b>			
Number of patients reporting events, n	9 (21%)	3 (7%)	0.05
Total number of adverse events, n	17	4	ns
- nausea	6	1	
- chills	4	0	
- headache	3	1	
- dizziness	1	1	
- chest pain	1	0	
- dysaesthesia	1	0	
- dysgeusia	1	0	
- diarrhoea	0	1	

p-values were calculated by  $\chi^2$  test or Mann Whitney U-test (number of events per patient), ns: not significant and no trend ( $p > 0.10$ ).

## Figure Legends

Figure 1: **Study flow diagram**

Figure 2: **Fatigue at baseline and after 6 weeks in the iron and the placebo group** (dotted lines correspond to medians of the groups).

Figure 3: **Change of fatigue in patients with baseline ferritin  $\leq 15$  ng/mL depending on the administration of iron or placebo** ( $p=0.005$ ).

**Figure 1**

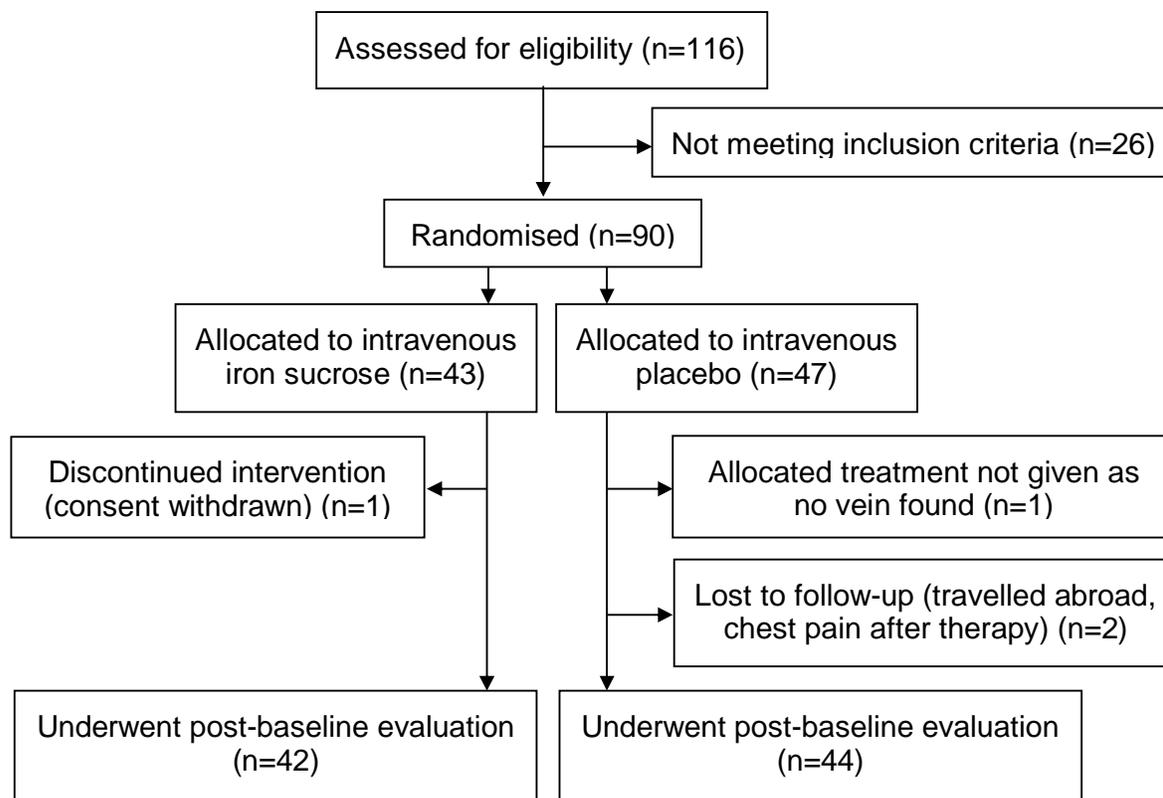


Figure 2

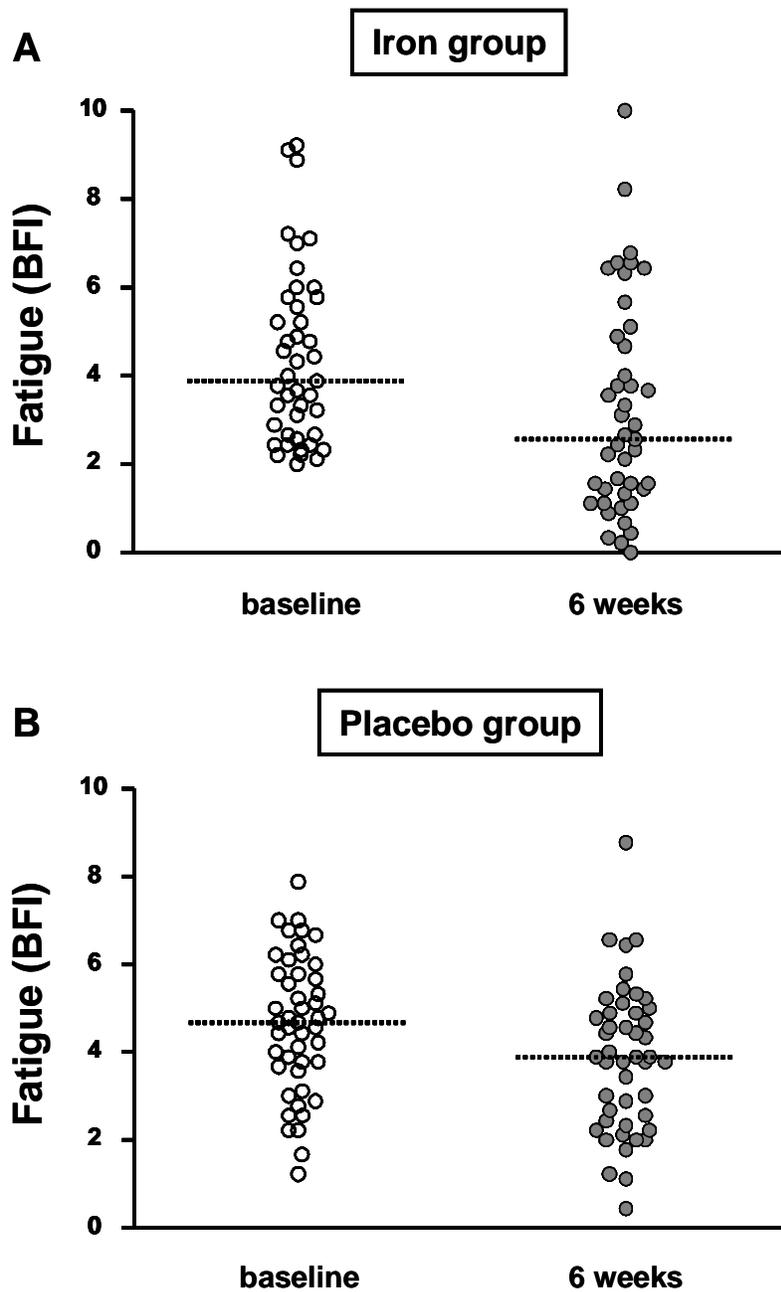


Figure 3

