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ORIGINAL CONTRIBUTION

Efficacy and tolerability of a prolonged release ferrous sulphate formulation in iron deficiency anaemia: a non-inferiority controlled trial

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Abstract
Background Iron deficiency anaemia (IDA) is the last stage of iron deficiency, consecutive to an imbalance between iron supply through food intake and iron loss through physiological or pathological processes. As well as by haemoglobin levels, IDA is diagnosed by measuring biomarkers of iron stores. Women are most affected by IDA since their teenage years, as menstruation constitutes a chronic iron loss. Oral supplementation with ferrous sulphate is an effective therapy, but gastrointestinal side effects may impair treatment compliance.
Methods The present multicentric randomised controlled trial was designed to assess the non-inferiority of a ferrous sulphate prolonged release formulation called V0355 with the referential ferrous sulphate Ferrograd® in a population of Italian women aged 18–50 years diagnosed for IDA. Three hundred and ninety-nine patients were randomised to receive V0355 (80 mg Fe/day) or Ferrograd® (105 mg Fe/day).
Results After 12 weeks of treatment, the difference in the mean haemoglobin level between the two groups was 0.081 g/dL ([−2.986;1.361], $p = 0.54$), which confirmed the hypothesis of non-inferiority. All the other biochemical parameters (serum iron, serum ferritin, transferrin, and soluble transferrin receptor) and haematological parameters (erythrocytes count, reticulocytes count, haematocrit, and mean corpuscular volume), as well as patient's anaemia-related symptoms, were not different between treatment groups throughout the study. Furthermore, the incidence of gastrointestinal adverse events of moderate and severe intensity was significantly lower ($p = 0.007$) in the V0355 group (5.6%) than in the Ferrograd® group (13.9%).
Conclusion V0355 was as efficient as Ferrograd® in the treatment of anaemia and exhibited a better gastrointestinal tolerance profile.

Keywords Iron deficiency anaemia · Ferrous sulphate · Gastrointestinal tolerance · Non-inferiority

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Introduction

Iron is an essential element for life, due to its central role in the transport of oxygen and as a common enzymatic cofactor. Excluding specific diseases, iron status represents a balance between nutritional input and physiological loss. With adequate nutrition, iron requirements for haemoglobin and many other proteins are fulfilled [1]. Furthermore, reserves of iron stored in tissues are available in case of insufficient iron absorption and also reflect iron nutritional status [2].

Iron deficiency occurs in three sequentially developing stages. The first stage is depleted iron stores with maintained haemoglobin level. The second stage is iron-deficient erythropoiesis, whereas haemoglobin concentration remains normal. The third and most severe form is iron deficiency anaemia (IDA), which develops when the iron

supply is inadequate for haemoglobin synthesis, resulting in subnormal haemoglobin concentrations [3].

IDA diagnosis requires concomitant anaemia and iron deficiency [4]. Anaemia is defined by a haemoglobin level lower than the age- and gender-specific level, which is 12 g/dL for non-pregnant women [5]. For the diagnosis of iron deficiency, the classic hallmarks are low serum ferritin (<30 μg/L), serum iron (SI) < 330 μg/L and serum total iron-binding capacity (TIBC) > 4 mg/L, resulting in transferrin saturation <20% [4]. The best laboratory test to diagnose IDA is serum ferritin, which, when less than 15 μg/L, has a specificity of 99% for the disease. However, ferritin is an acute-phase reactant and is poorly indicative in case of infectious or inflammatory disease [6, 7]. In clinical practice, it is assumed that a low haemoglobin concentration in a patient with a serum ferritin <30 μg/L is indicative of IDA [4].

Diet sometimes fails to meet iron requirements, particularly during infancy and pregnancy. Anaemia may be aggravated by deficiencies in other micronutrients (folates, vitamin B_{12} and vitamin A) or concomitant diseases (parasitic infections, thalassaemia, etc.) [8]. The underlying causes of IDA are commonly physiological. The prevalence of iron deficiency rises in adolescent females when menstrual iron loss becomes superimposed on growth requirements and lasts during adulthood [2]. Pathological IDA is invariably due to excessive blood loss, mostly from the gastrointestinal tract and the uterus in women. Other causes of iron deficiency are impairment of gastrointestinal absorption [3, 4]. IDA is one of the most widespread public health problems and has a major impact on health and welfare and on social and economic issues. These include reduced growth and increased morbidity in children [5, 9], impaired cognitive development [10], reduced work capacity [11] and, in severe cases, increased risk of mortality during the perinatal period [12].

Oral iron is widely used to treat iron deficiency. Ferrous sulphate is the preferred form of oral iron because of low cost and high bioavailability. However, the major difficulty encountered with oral iron intake is gastrointestinal tolerability, mainly nausea and epigastric discomfort, that occurs shortly after ingestion. These symptoms vary in proportion to the concentration of ionisable iron in the upper gastrointestinal tract. Any reduction in symptoms is invariably due to a parallel decrease in iron absorption and consequently in treatment efficacy [4, 9, 13].

The present trial was promoted to assess a formulation of prolonged release ferrous sulphate in comparison with the referential ferrous sulphate Ferrograd® (Abbott, Illinois, USA). This new ferrous sulphate formulation (V0355) was developed to avoid massive release of iron in the gastrointestinal tract, thus increasing the tolerance and efficacy of the treatment. The study was designed as a non-inferiority randomised trial to assess whether both treatments presented similar efficacy profiles and risk/benefit ratio with regard to the pathophysiological effects of IDA in women of childbearing potential [2]. The drug V0355 was expected to be as efficient as Ferrograd® and to exhibit a better tolerability profile when administered under usually recommended conditions [5, 8]. The study was designed for this purpose.

Patients and methods

Trial design

The study was a multicenter, prospective, randomised, controlled, parallel, non-inferiority study performed in patients with IDA over a 12-week period [14]. The trial was carried out in accordance with Good Clinical Practices, local laws and regulations and was approved by the Ethics Committee of Umbria (Perugia, Italy) and registered at www.pfclintrial.com, No. V00355 CP 301 3A.

Participants

The study planned to include 400 ambulatory females between 18 and 50 years with IDA, diagnosed by a haemoglobin level between 9 and 12 g/dL and a serum ferritin level <30 μg/L. The main exclusion criteria were as follows: anaemia related to causes other than iron deficiency (inflammation, marrow failure, haemopathies, acute haemorrhage or chronic renal failure); diseases such as haemochromatosis, gastroduodenal ulcer, inflammatory bowel disease or any digestive disease, which could modify iron absorption; any previous or concomitant treatment known to modify physiological iron status. Women of childbearing potential not using effective contraception, pregnant, breast-feeding or likely to become pregnant during the time of the study were excluded. The patients were recruited in 66 centres of primary care physicians in Italy.

Interventions

The patients went through the screening visit, then the inclusion visit within 1 week. After checking inclusion and exclusion criteria and signing informed consent, patients were centrally randomised via an interactive voice response system (IVRS) into 2 treatment groups: V0355 and Ferrograd®. The control treatment is the reference treatment for anaemia in Italy, as indicated in the Summary of Product Characteristics of Ferrograd®.

Patients self-administered one tablet per day of the investigational drug for 12 weeks. It was to be swallowed

daily in the morning before taking any food. V0355 contained 80 mg and Ferrograd® contained 105 mg of elemental iron per tablet. Patients were informed not to take any food (tea, coffee and wine) or drugs (calcium, magnesium or aluminium salts, oxides and hydroxides, cyclins, penicillamine, fluoroquinolones, bisphosphonates and thyroxine) modifying iron absorption concomitantly with the study drug.

Two follow-up visits were planned after inclusion at weeks 4 and 8. The study end visit was planned for week 12. A blood sample was withdrawn at each visit through puncture of a peripheral vein in the forearm.

Objectives

The primary objective of this study was to demonstrate the non-inferiority of V0355 *versus* Ferrograd® on the restoration of haemoglobin levels after a 12-week treatment in adult women from 18 to 50 years old with IDA. The secondary objectives were to assess efficacy in terms of iron store restoration, improvement in anaemia-related symptoms and quality of life and to assess safety in terms of gastrointestinal tolerability as well as global tolerability.

Both investigational products delivered ferrous sulphate at the dose included in the World Health Organisation (WHO) daily dose range recommended to treat IDA in adults, for a period also according to recommendations [5]. Therefore, the non-inferiority hypothesis was considered the primary objective.

Outcomes

The primary assessment criterion was the comparison between the two treatment groups of mean haemoglobin levels after a 12-week treatment. Haemoglobin level is the relevant parameter for evaluating the efficacy of oral iron in IDA.

The secondary outcomes were measured by comparing iron-related biochemical parameters (haemoglobin, serum iron, serum ferritin, transferrin, transferrin saturation, and soluble transferrin receptor) and haematological parameters (erythrocytes, reticulocytes, haematocrit and mean corpuscular volume (MCV)) at each visit; the evolution of the patient's anaemia-related symptoms (fatigue, pallor, dyspnoea, nail disorders, loss of appetite, deterioration in cognitive functions and skin disorders) at each visit; the mean changes in Physical Component Summary (PCS) and Mental Component Summary (MCS) of SF12 health survey [15] after a 12-week treatment.

Safety and tolerability were assessed by occurrence of adverse events (AEs). Particular attention was paid to gastrointestinal AEs of moderate and severe intensity (abdominal pain, nausea, vomiting, regurgitation, diarrhoea and constipation), frequently reported with oral iron therapy.

Blood analyses were performed by a central laboratory to reduce measurement variability. Other data related to the assessment of secondary outcomes were collected on site at each visit to primary care centres.

Sample size

Assuming a non-inferiority margin of 0.4 g/dL for the mean haemoglobin level and a standard deviation of 1.1 g/dL, taking a one-sided alpha risk of 2.5% and a power of 90%, 160 patients per treatment group were required. Based on an estimated rate of 20% of patients excluded from the per-protocol analysis, 200 patients were planned to be enrolled in each group.

Randomisation

Treatment units were provided by the Clinical Pharmacy Department of the study sponsor. At the inclusion visit, the investigator called the IVRS to allocate a treatment number to each patient.

Blinding

An open-label design was acceptable because the potential biases of not using a double-blind procedure were minimised using (1) objective biological parameters as assessment criteria; (2) central randomisation for treatment assignment; and (3) a central laboratory blinded to treatment assignment for haematological analysis.

Statistical methods

The Safety data set was composed of all randomised patients having received at least one dose of the study medication; the full analysis set (FAS) was composed of all treated patients, with a posteriori serology-confirmed diagnosis, with at least one post-baseline evaluation of haemoglobin level; the per-protocol set (PP) excluded patients with at least one major protocol deviation. For the FAS and PP analyses, missing evaluations of efficacy criteria at week 12 were replaced by the last observation available.

Quantitative and qualitative parameters were described by treatment group using current descriptive statistics. The Wilcoxon statistical test compared treatment groups at inclusion.

The primary efficacy analysis of the primary criterion was a non-inferiority test. The lower limit of the 95% confidence interval (with a one-sided alpha risk of 2.5%) of the difference between test and reference drugs was

compared with the margin of 0.4 g/dL. The primary analysis was conducted on the PP and then confirmed on the FAS, as recommended [14].

All the secondary criteria were analysed in both FAS and PP. At each visit, changes from baseline were compared between treatment groups using either the Student's test or the Wilcoxon test, depending on whether data were normally distributed or not. Fisher's exact test compared the incidence of treatment-emergent gastrointestinal AEs of moderate and severe intensity.

Results

Study flow chart

See Fig. 1.

Recruitment

The first patient was recruited on 29 February 2008, and the last patient follow-up was completed on 31 March 2009.

Baseline data

No statistically significant difference was observed between treatment groups regarding demography and IDA characteristics (Table 1). None of the medical and surgical histories of patients were expected to interfere with investigational product assessment.

Numbers analysed

The FAS included 185 of 198 (93.4%) randomised patients for V0355 group and 174 of 201 (86.6%) for Ferrograd® group. The PP included 165 of 185 (89.2%) randomised

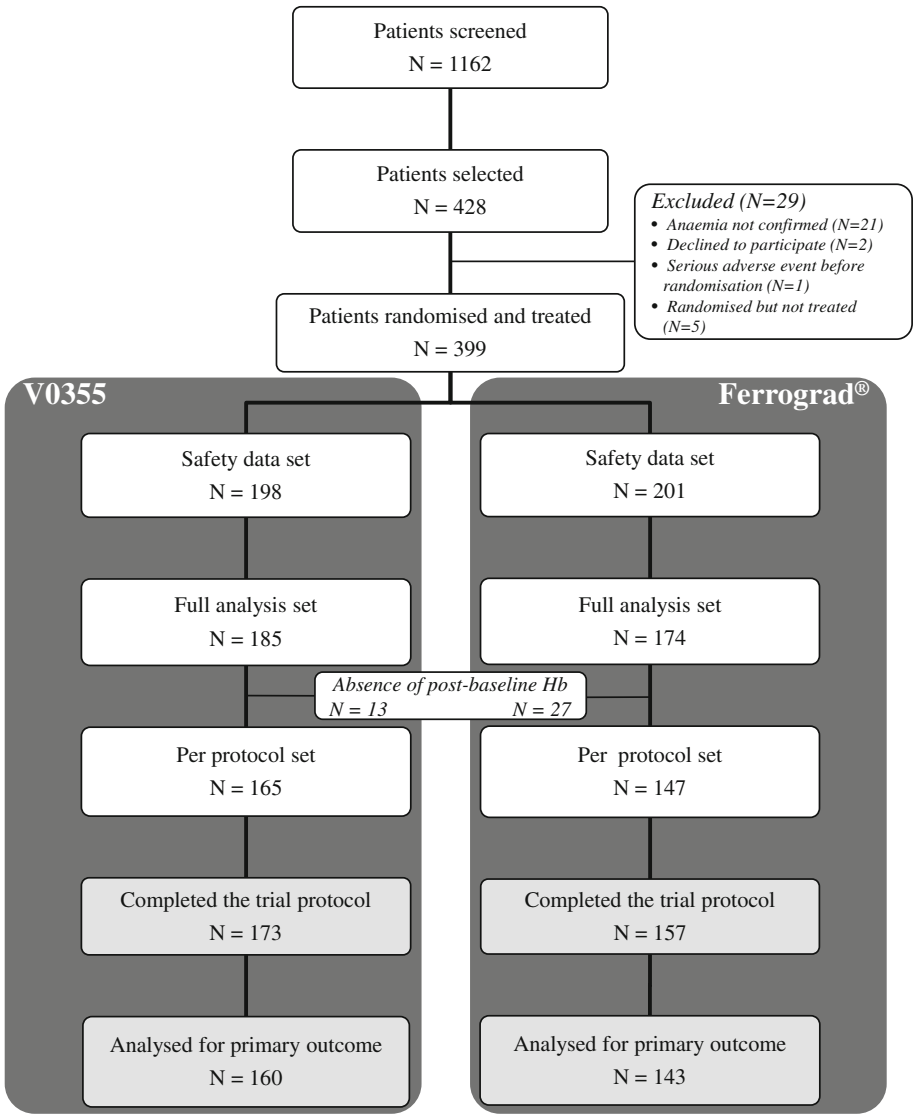

Fig. 1 Study flow chart

Table 1 Baseline characteristics of the PP data set

	V0355 $n = 165$	Ferrograd® $n = 147$	Normal ranges
Age (Years)			–
Mean (SD)	40.6 (7.6)	41.1 (7.3)	–
Min/Max	19/51	19/51	–
Body mass index by class (Kg/m^2)			–
<25	121 (73.3%)	103 (70.1%)	–
[25–30[	34 (20.6%)	31 (21.1%)	–
≥30	10 (6.1%)	13 (8.8%)	–
Parameters related to anaemia			
Haemoglobin (g/dL)	10.56 (0.99)	10.71 (0.92)	12.00–16.00
Haematocrit (%)	32.6 (2.4)	32.7 (2.2)	36.0–46.0
Erythrocytes (10^{12}/L)	4.15 (0.34)	4.19 (0.37)	4.00–5.20
Reticulocytes (10^9/L)	57 (37)	59 (27)	20–100
MCV (fL)	78.70 (7.49)	78.74 (7.83)	79.00–97.00
Parameters related to iron			
Ferritin (μg/L)	6.56 (5.34)	7.61 (5.87)	30.00–120.00
Transferrin (g/L)	3.25 (0.50)	3.35 (0.59)	2.00–3.80
Transferrin saturation (%)	14.0 (13.6)	13.9 (13.8)	20.0–55.0
Soluble transferrin receptor (mg/L)	2.41 (0.94)	2.37 (1.12)	0.76–1.76
Serum iron (μmol/L)	9.64 (8.77)	9.84 (8.90)	9.00–27.00

All values are expressed as mean (SD) except for body mass index that is expressed as number of patients (% of patients per group). Minimal and maximal values are also presented for haemoglobin

patients for V0355 group and 147 of 174 (84.5%) for Ferrograd® group.

Outcomes

The haemoglobin levels throughout the 12 weeks of treatment are shown in Table 2 and Fig. 2 for the PP. The lower limit of the 95% CI of the difference between V0355 and Ferrograd® was higher than the predefined 0.4-point limit for non-inferiority on both PP and FAS. The primary objective of the study was thus met, and V0355 was demonstrated non-inferior to Ferrograd® to increase haemoglobin level in women with IDA. Furthermore, haemoglobin levels were highly improved from week 4 in both groups. The mean threshold value of 12 g/dL haemoglobin was reached after 8-week treatment with both products (Fig. 2).

The secondary efficacy criteria consisted in the evolution of iron-related biochemical and haematological parameters during treatment (Table 2). No statistically significant difference was observed between V0355 and Ferrograd® treatment groups for all haematology and biochemical iron parameters (see Fig. 3 for ferritin).

All the evaluated parameters confirmed the non-inferiority of V0355 compared with Ferrograd®. All investigated IDA-related symptoms improved, with no clinically relevant difference across treatment groups. Anaemia-related symptoms progressively improved during treatment. The most frequent symptoms at baseline (fatigue and pallor) improved slightly more frequently over treatment in the V0355 group (see Fig. 4). Similarly, mental and physical components of the SF-12 survey were improved at the end of study. In the PP data set, the mean physical score improved by 3.4 and 4.3 points in the V0355 group and the Ferrograd® group, respectively, between baseline and the last visit. The mean mental score improved simultaneously by 5.5 and 6.3 points. The difference between groups was not statistically significant. Clinical improvement was observed from week 4 onwards with both products.

Adverse events

The overall extent of exposure ranged from 3 to 134 days, with a mean (SD) of 81.5 (25.4) days, and was not different across treatment groups.

A total of 226 AEs were recorded throughout the study in 174 patients, 217 of which were classified as treatment-emergent adverse events (TEAEs) in 131 patients. The details of AEs by study group (expressed as the number of affected patients) are provided in Table 3. Overall, 30 patients (7.5%) interrupted the treatment due to the occurrence of AEs. No clinically relevant difference

Table 2 Haematology and iron store parameters at the end of study

	V0355	Ferrograd®	Difference [95% CI]
Number of observations (PP data set)	165	147	
Haemoglobin level (g/dL)	12.53 (0.96)	12.61 (0.99)	−0.081
Min/Median/Max	8.9/12.6/14.6	9.5/12.6/16.1	[−0.299;0.136]
			$p = 0.54$
Haematocrit (%)	37.5 (2.7)	37.7 (2.8)	$p = 0.95$
Erythrocytes (10^{12}/L)	4.33 (0.37)	4.35 (0.36)	$p = 0.75$
Reticulocytes (10^{9}/L)	47 (22)	46 (20)	$p = 0.33$
MCV (fL)	86.89 (5.51)	86.94 (5.54)	$p = 0.65$
Ferritin (μg/L)	19.82 (10.39)	22.57 (10.77)	$p = 0.07$
Transferrin (g/L)	2.60 (0.44)	2.65 (0.48)	$p = 0.31$
Transferrin saturation (%)	24.0 (10.9)	24.3 (13.3)	$p = 0.73$
Soluble transferrin receptor (mg/L)	1.32 (0.46)	1.34 (0.50)	$p = 0.24$
Serum iron (μmol/L)	13.53 (5.72)	13.79 (7.03)	$p = 0.65$

All values are expressed as mean (SD) and minimal, median and maximal values for haemoglobin

"End of study" is defined as the last observation carried out for each patient

Difference is expressed for haemoglobin. For other parameters, p value indicates the probability of inter-group difference, as assessed by Student's t test (normally distributed data) or nonparametric Wilcoxon test (used otherwise)

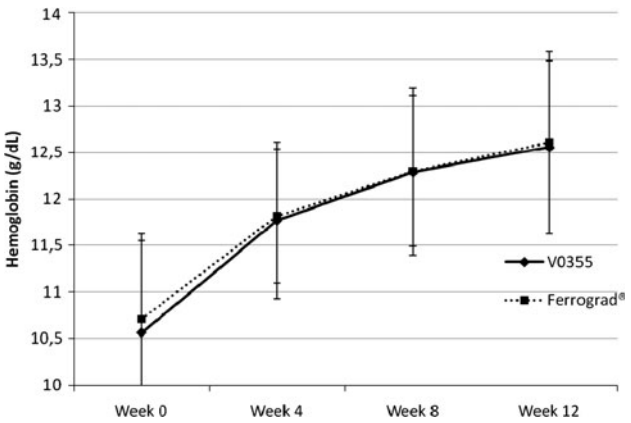

Fig. 2 Evolution of mean haemoglobin levels (g/dL) during treatment for the PP data set. No difference between treatment groups for change between baseline and each follow-up visit ($p > 0.30$, Wilcoxon test)

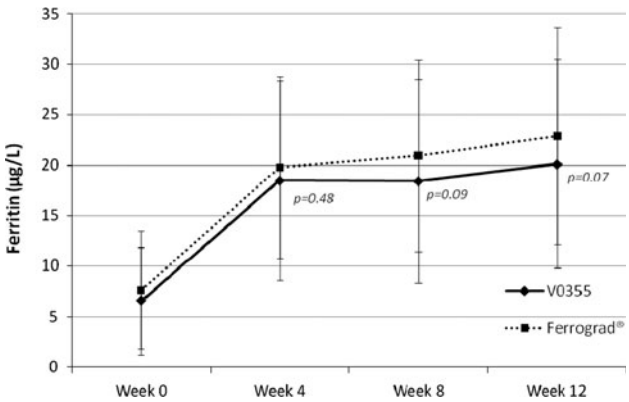

Fig. 3 Evolution of mean ferritin levels (μg/L) during treatment for the PP data set. No difference between treatment groups for change between baseline and each follow-up visit (p values indicated, Wilcoxon test)

between treatment groups was observed in the number, relationship to study drug and intensity of SAEs and AEs leading to definitive study drug discontinuation.

The most frequent TEAEs considered to be related to the study drug, regardless of their intensity, were gastrointestinal (GI) disorders in both treatment groups (17.7 and 21.9% in V0355 and Ferrograd® groups, respectively). The incidence of prespecified GI TEAEs of moderate and severe intensity was significantly lower ($p = 0.007$) in the V0355 group (11 patients, 5.6%) than in the Ferrograd® group (28 patients, 13.9%). None of the 198 women included in the V0355 group complained of moderate or severe intensity nausea, vomiting, constipation or dyspepsia; only one suffered from moderate diarrhoea (see Table 4), whereas 14 patients in the group of 201 women receiving Ferrograd® experienced one of these disorders. Consequently, fewer women in the V0355 group than in the Ferrograd® group used concomitant drugs targeted to the alimentary tract (5.6 vs. 10.0%). The groups did not differ in number or intensity or relationship to study drug regarding other TEAEs.

Overall, 3 serious adverse events (SAEs) were recorded in 2 patients receiving V0355 and 5 SAEs in 5 patients receiving Ferrograd®; all recovered without sequelae. The relationship to study drug was excluded for all SAEs, except for one case of appendicitis in a patient who received V0355.

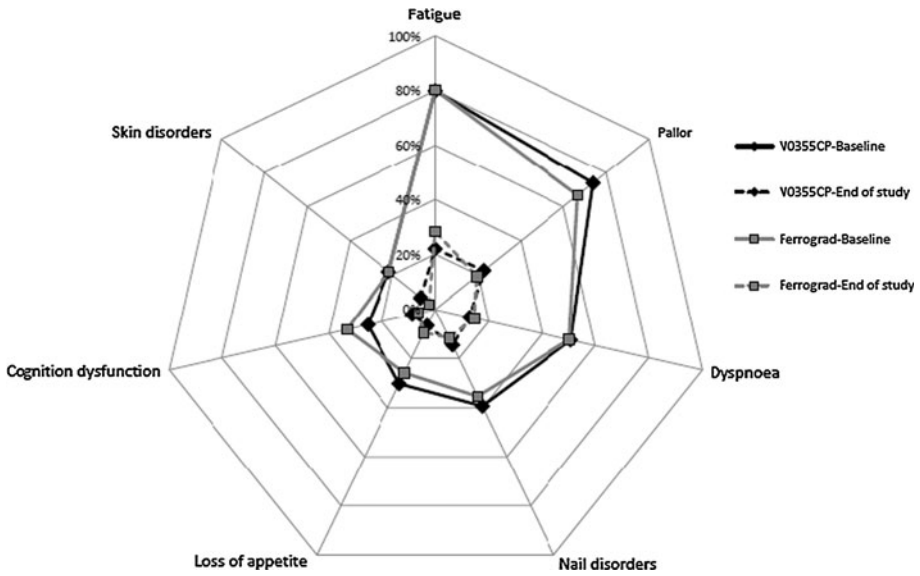

Fig. 4 Prevalence of anaemia-related symptoms at baseline and at the end of the study for the PP data set. "End of study" is defined as the last observation carried out for each patient

Table 3 Summary of adverse events recorded in the Safety data set

	V0355 $n = 198$	Ferrograd® $n = 201$
AEs	62 (31.3%)	72 (35.8%)
Including those leading to permanent study drug discontinuation	12 (6.1%)	18 (9.0%)
TEAEs	62 (31.3%)	69 (34.3%)
Including GI disorders	35 (17.7%)	44 (21.9%)
Including GI disorders of moderate and severe intensity	11 (5.6%)	28 (13.9%)**
TEAEs associated to study drug	39 (19.7%)	54 (26.9%)
Including GI disorders	33 (16.7%)	43 (21.4%)

Expressed as the number and % of patients experiencing at least one AE during the study

** Significantly different between groups ($p = 0.007$)

Table 4 Treatment-emergent gastrointestinal AE of moderate or severe intensity in the Safety data set

	V0355 $n = 198$	Ferrograd® $n = 201$
Gastrointestinal disorders	11 (5.6%)	28 (13.9%)
Gastrointestinal disorder (at least one symptom)	3 (1.5%)	8 (4.0%)
Upper abdominal pain	3 (1.5%)	4 (2.0%)
Abdominal pain	2 (1.0%)	5 (2.5%)
Diarrhoea	1 (0.5%)	3 (1.5%)
Gastrointestinal motility disorder (at least one symptom)	1 (0.5%)	–
Nausea	–	4 (2.0%)
Vomiting	–	3 (1.5%)
Constipation	–	2 (1.0%)
Dyspepsia	–	2 (1.0%)
Gastroenteritis	1 (0.5%)	–

Expressed as the number and % of patients experiencing at least one treatment-emergent AE during the study

Discussion

The study was designed to assess whether two ferrous sulphate preparations presented similar efficacy profiles and risk/benefit ratio with regard to the known patho-physiological effects of IDA.

The study demonstrated the non-inferiority of V0355 vs. Ferrograd® on the restoration of haemoglobin levels after 12-week treatment in women of childbearing potential with IDA. It confirmed that oral ferrous sulphate is an efficient treatment for IDA, as it has been widely used for more than 30 years with a favourable safety profile [4].

V0355 tended to be slightly superior to Ferrograd® in the resolution of fatigue and pallor. The efficacy and time-course for all haematological and biochemical parameters investigated were similar with both products. As expected, soluble transferrin receptor decreased during the study, reflecting the decrease in erythropoiesis-related iron demand [16, 17]. Therefore, it can be assumed that women participating in this study recovered from anaemia, but were still on the way to recovering from iron deficiency because their body iron stores remained incomplete at the end of the follow-up, according to consensual diagnosis criteria [4]. They should benefit from prolongation of iron supplementation. Those observations are consistent with previous studies and recommendations, which indicate that anaemia should be corrected within 2-4 months with appropriate doses of iron and that therapy should continue for an additional 4–6 months to replenish iron stores [18].

A similar efficacy pattern for the two products on primary and secondary end points was obtained, whilst their ferrous sulphate content was different. Indeed, V0355 contained 80 mg elemental iron, i.e. 24% less than Ferrograd® that contained 105 mg. It can thus be assumed that the non-inferiority of V0355 is explained by the better absorption rate of iron compared with Ferrograd®. The pharmaceutical laboratory manufacturing V0355 selected up-to-date excipients and technology for this purpose. The new ferrous sulphate formulation (V0355) was developed in order to achieve a dissolution profile that corresponds to a sustained-release formulation (data not shown). The aim is to avoid massive release of iron in the gastrointestinal tract, thus increasing the efficacy (via presumed improved bioavailability) of the medicinal product. Another advantage of a sustained-release formulation is that it is likely to be taken with meals, thus improving the safety profile whilst maintaining the efficacy.

GI disorders are among the most frequently observed side effects in women receiving oral ferrous sulphate for IDA [5, 9]. They are attributable to a toxic effect of iron on the gastroduodenal mucosa [19]. As expected, in the present study, the most frequent side effects concerned the GI tract. Nevertheless, in the conditions of this clinical trial, V0355 produced significantly less moderate or severe GI side effects than Ferrograd®. This difference demonstrated the improved GI tolerance of V0355 compared with Ferrograd®, which was coupled with reduced use of concomitant drug for GI disorders. As intolerance of oral iron supplements is mainly related to the amount of soluble iron in the GI tract [13], the improved tolerance of V0355 could be attributable to the lower amount of iron, together with prolonged release, smoothing the peak concentration of iron and thus preventing mucosal irritation. Improved tolerance is beneficial since side effects are linked to poor treatment compliance [5]. In this study, compliance was 95.1 and 93.4% in V0355 and Ferrograd® groups, respectively.

Women of childbearing age are pointed out by the WHO as a vulnerable population with regard to iron deficiency. They often present a negative iron balance. Indeed, pregnancy increases the risk of IDA due to the iron requirements of the foetus and the expansion of maternal red cell mass [2]. The primary care centres participating in this study were frequented by young women representative of the Italian non-pregnant female population. The 400 patients required to demonstrate the non-inferiority of the investigational drug in comparison with the reference product were easily recruited by general practitioners. This population was large enough to bring out the improved GI tolerability of V0355, even if the trial was not primarily designed for this objective.

By demonstrating the equal efficacy and better tolerance of V0355 in comparison with Ferrograd® for women of childbearing age with IDA, this study suggests that V0355 indications could be extended (e.g. management of physiological IDA in the population of pregnant and breast-feeding women). In pathological IDA due to gastrointestinal or genital bleeding, or chronic kidney disease, requiring long-term ferrous treatment, the use of a low side-effect drug would also be beneficial [20, 21].

Conclusion

Overall, the study demonstrated that the efficacy of V0355 (80 mg elemental iron per day) to restore haemoglobin levels was not inferior to that of Ferrograd® (105 mg per day) when administered for 12 weeks to women of childbearing potential suffering from IDA. A strong tendency towards increased body iron stores was observed, with similar efficacy and time-course for both treatments investigated. All IDA-related symptoms gradually improved over the treatment period, and the SF12 survey suggested an improvement in mental and physical performances. Both V0355 and Ferrograd® exhibited good overall tolerance. However, GI tolerance was significantly better in the V0355 group than in the Ferrograd® group.

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Conflict of interest Dr Piselli received research support for this study from Institut de Recherche Pierre Fabre. Dr Fioravanti is the CEO of the CRO in charge of the study and received fees for this service. Dr Zaim and Mrs Kanony-Truc are employees of Institut de Recherche Pierre Fabre, which provided financial and material support for the design and concept of the study, data collection, data management, data analysis and the publication of this study.

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