**Pierre Fabre Médicament**
**Represented by: Institut de Recherche Pierre Fabre**
**45, Place Abel Gance**
**F-92654 Boulogne Cedex**

# 1. TITLE PAGE

# CLINICAL STUDY REPORT

## EFFICACY AND TOLERABILITY OF 12-WEEK ORAL TREATMENT WITH V0355 VERSUS FERROGRAD® IN IRON DEFICIENCY ANAEMIA

***A MULTICENTER, RANDOMISED, OPEN-LABEL TRIAL***

**Investigational product**: **V0355**

**Protocol number**: V00355 CP 301 3A

**Phase of development**: **PHASE III**

**Date of first enrolment**: 29/02/2008

**Date of last completed**: 31/03/2009

**Co-ordinator(s)**: Dr Leonardo PISELLI, Via Flamimia, 43, 06049 Spoleto (PG), Italy

**Sponsor Representative(s) for study report**: Clinical Study Coordinator: Myriam CONDOMINES, +33 (0)5 61 73 73 28

**Date of report**: 26-Apr-2010

Study performed in compliance with Good Clinical Practice.

# 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Company: Pierre Fabre Médicament** | **Individual Study Table** | **(For National Authority Use Only)** |
| **Name of finished product:** **V0355** | **Referring to Module 5 of the Dossier** | |
| **Name of active ingredient:** **Ferrous sulphate** | **Vol.: .....Page: .....** | |

| | | |
|---|---|---|
| **Title of study:** | Efficacy and tolerability of 12-week oral treatment with V0355 versus FERROGRAD® in iron deficiency anaemia. A multicentre, randomised, open-label trial. | |
| **Investigators:** | DR Leonardo PISELLI - Via Flamimia, 43 - 06049 Spoleto (PG), Italy | |
| **Study centre(s):** | The study was conducted by primary care physicians in Italy. | |
| **Publication (reference):** | Not applicable | |
| **Studied period** *(years, months ...)*: **(date of first enrolment)** **(date of last completed)** | First enrolment: 29/02/2008<br>Last completed: 31/03/2009 | **Phase of development:**<br>III |
| **Objectives:** **Primary:** **Secondary:** | Primary objective:<br>To demonstrate non-inferiority of V0355 versus FERROGRAD® on haemoglobin level restoration after 12-week treatment in iron deficiency anaemia.<br>Secondary objectives:<br>To assess the efficacy on:<br>- Iron stores restoration,<br>- patient's anaemia related symptoms,<br>- patient's quality of life improvement,<br>To evaluate the gastrointestinal and the global tolerability of the products. | |
| **Methodology:** | Prospective, multicentre, randomised, parallel group, open-label trial.<br>Five visits were planned: screening visit (V1), inclusion visit (V2), follow-up 1 (V2, 4 weeks after V2), follow-up 2 (V3, 8 weeks after V2) and end-of-study visit (V5, 12 weeks after V2). | |
| **Number of patients (planned and analysed):** | 400 female patients between 18 and 50 years were planned (200 patients per group), 399 were treated (198 in the V0355 group and 201 in the FERROGRAD® group), 359 patients (185 in the V0355 group and 174 in the FERROGRAD®) in the full analysis set and 312 patients (165 in the V0355 group and 147 in the FERROGRAD® group) were evaluated in the per protocol analysis. | |
| **Diagnosis and main criteria for inclusion:** | Were included in the study those patients who met the following criteria:<br>- Ambulatory females between 18 and 50 years with iron deficiency anaemia1:<br>  o haemoglobin level between 90 g/L and 120 g/L,<br>  o serum ferritin level < 30 µg/L);<br>- Able to understand the protocol, comply with its requirements and attend at visits, likely to be compliant during the study; according to the judgment of the Investigator, and having given written informed consent for willing to participate;<br>- If required by local regulations, registered with a social security or health insurance system. | |
| **Test product, Dose, Mode of administration, Batch number:** | V0355 – 247.25 mg dried ferrous sulphate (equivalent to 80 mg elemental iron), oral administration, 1 tablet once a day before food every morning, batch Nr SB0474. | |
| **Other product, Dose, Mode of administration, Batch number:** | Not applicable | |
| **Duration of treatment:** | Study drugs had to be taken orally, once a day during 12 weeks ± 7 days. | |



[1] A confirmation of the diagnosis of iron deficiency anemia was obtained by the central laboratory analysis at the inclusion visit.

| **Name of Company: Pierre Fabre Médicament** | **Individual Study Table** | **(For National Authority Use Only)** |
|---|---|---|
| **Name of finished product:** **V0355** | **Referring to Module 5 of the Dossier** | |
| **Name of active ingredient:** **Ferrous sulphate** | **Vol.: .....Page: .....** | |

| | |
|---|---|
| **Reference therapy,**<br>**Dose,**<br>**Mode of administration,**<br>**Batch number:** | FERROGRAD® - 525 mg dried ferrous sulphate (equivalent to 105 mg elemental iron), 1 tablet once a day before food every morning, batch Nr 46577TF02. |
| **Criteria for evaluation:**<br>**Efficacy::** | **Primary assessment criterion:**<br>Comparison between the 2 groups of the mean haemoglobin level after 12-week treatment,<br>**Secondary criteria:**<br>- comparison between the 2 groups of the mean ferritin level after 12-week of treatment,<br>- evolution of the haematological parameters from baseline to visits 3, 4 and 5 (serum iron, serum ferritin, transferrin, transferrin saturation, soluble transferrin receptor, erythrocytes count, reticulocytes count, haemoglobin, haematocrit, mean corpuscular volume),<br>- evolution from baseline of patient's anaemia related symptoms at visits 3, 4 and 5,<br>- mean changes of Physical Component Summary (PCS) and Mental Component Summary (MCS) of SF12, between baseline and visit 5. |
| **Safety** | **Criteria for tolerability evaluation:**<br>- Percentage of patients reporting at least one adverse event for each treatment group,<br>- Percentage of patients reporting at least one moderate to severe gastrointestinal adverse event for each treatment group. |
| **Statistical methods:** | **Sample size calculation:**<br>Assuming a non-inferiority margin of 4 g/L for the mean haemoglobin level, and a standard-deviation of 11 g/L, and taking a one-sided risk alpha of 2.5%, 160 patients without major deviations were required per treatment group to demonstrate non-inferiority with a power of 90%.<br>Based on an estimated rate 20% of patients excluded from the per-protocol analysis, it was planned that 400 patients would be enrolled (200 in each group).<br>**Statistical analysis:**<br>Comparability of the 2 groups regarding demographic characteristics and the haematological parameters at inclusion by parametric or non-parametric tests, as appropriate.<br>**Primary criterion**<br>Main efficacy analysis was performed on the Per Protocol (PP) population dataset.<br>The lower limit of the 95% confidence interval of the difference between test and reference drug was compared to the non-inferiority margin: if this limit was above – 4 g/L, V0355 was to be declared non-inferior to FERROGRAD®.<br>The same analysis was performed on the Full Analysis Set (FAS) population as a confirmatory analysis.<br>**Secondary criteria:**<br>Since it is difficult to define non-inferiority margins for secondary criteria, the analyses were performed using statistical tests for differences between V0355 and FERROGRAD®. All criteria being quantitative, either the Student or the Wilcoxon test were used, as appropriate. |
| **Statistical methods (continued):** | **Safety analysis**<br>Descriptive analysis of adverse events according to MedDRA classification. Fisher's exact test for comparing the incidence of gastrointestinal adverse events. Descriptive analysis of clinically significant abnormal values for biochemistry and vital signs. |

| Name of Company: Pierre Fabre Médicament | Individual Study Table | (For National Authority Use Only) |
|---|---|---|
| Name of finished product: V0355 | Referring to Module 5 of the Dossier | |
| Name of active ingredient: Ferrous sulphate | Vol.: .....Page: ..... | |

**Summary - Conclusions:**

**Efficacy results**

The demographic characteristics of the population for the PP data set are summarized below:

| | V0355 N=165 | FERROGRAD® N=147 | TOTAL N=312 |
|---|---|---|---|
| **Age** (years) – Mean (SD) | 40.6 (7.6) | 41.1 (7.3) | 40.8 (7.5) |
| **Weight** (kg) - Mean (SD) | 64.46 (11.09) | 63.26 (12.15) | 62.84 (11.59) |
| **Height** (cm) - Mean (SD) | 163.8 (6.3) | 163.0 (6.9) | 163.4 (6.5) |
| **BMI** (Kg/m²) - Mean (SD) | 23.30 (4.21) | 23.84 (4.53) | 23.56 (4.36 |

The Wilcoxon test between both study groups did not reveal any statistically significant difference across demographic characteristics. The treatment groups can therefore be considered comparable regarding their demographic characteristics.

The mean (SD) values at baseline of anaemia- and iron store-related parameters investigated are summarized in the table below.

| | | V0355 n=165 | FERROGRAD n=147 |
|---|---|---|---|
| **Parameters related to anaemia** | Haemoglobin (g/L) | 105.6 (9.9) | 107.1 (9.2) |
| | Haematocrit (%) | 32.6% (2.4) | 32.7% (2.2) |
| | Erythrocytes (T/L) | 4.15 (0.34) | 4.19 (0.37 |
| | MCV (fL) | 78.70 (7.49) | 78.74 (7.83) |
| | MCH (pg) | 25.55 (3.02) | 25.78 (3.02) |
| **Parameters related to iron store** | Ferritin (µg/L) | 6.6 (5.3) | 7.6 (5.9) |
| | Transferrin (g/L) | 3.3 (0.5) | 3.4 (0.6 |
| | Transferrin saturation (%) | 14% (14) | 14% (14) |
| | Soluble transferrin receptor (mg/L) | 2.4 (0.9) | 2.4 (1.1) |

These results demonstrate the occurrence of iron-deficiency anaemia in the population studied.

The mean (SD) treatment compliance was 95.10% (6.88%) in the V0355 group and 93.43% (10.19%) in the FERROGRAD® group.

The results of the primary analysis of haemoglobin levels in the PP and FAS data sets at V5 (LOCF) are summarized below in for both treatment groups, together with values of the mean differences FERROGRAD® minus V0355 and its 95% CI.

| Haemoglobin Levels (g/L) at V5 (LOCF) | | V0355 | FERROGRAD® | Difference [95% CI] |
|---|---|---|---|---|
| **PP data set** | Number of available data | 165 | 147 | -0.813 |
| | Mean (SD) | 125.25 (9.619) | 126.06 (9.871) | [-2.986; 1.361] |
| **FAS** | Number of available data | 185 | 174 | -0.701 |
| | Mean (SD) | 124.0 (9.654) | 125.6 (10.131) | [-2.754; 1.353] |

The primary objective of the study was met, as these results in the PP data set at V5 demonstrated the non-inferiority of V0355 compared to FERROGRAD®. The levels of haemoglobin were consistently similar across both treatment groups. The results were confirmed in the FAS data set, with values of differences between both study groups very similar to those observed in the PP data set.

| Name of Company: Pierre Fabre Médicament | Individual Study Table | (For National Authority Use Only) |
|---|---|---|
| Name of finished product: V0355 | Referring to Module 5 of the Dossier | |
| Name of active ingredient: Ferrous sulphate | Vol.: .....Page: ..... | |

The results regarding the analysis of the evolution of haemoglobin levels in the PP data set are summarized in the table below for both study groups, together with the value of the mean difference FERROGRAD® minus V0355 and its 95% CI.

| Haemoglobin Level (g/L) | | V0355 n=165 | FERROGRAD® n=147 | Difference [95% CI] |
|---|---|---|---|---|
| **Follow-up 1 (V3)** | Number of available data | 164 | 146 | -0.427 |
| | Mean (SD) | 117.74 (8.382) | 118.16 (7.243) | [-2.188; 1.335] |
| **Follow-up 2 (V4)** | Number of available data | 164 | 146 | -0.111 |
| | Mean (SD) | 122.9 (9.049) | 123.01 (8.11) | [-2.041; 1.819] |
| **End of study (V5)** | Number of available data | 160 | 143 | -0.425 |
| | Mean (SD) | 125.64 (9.268) | 126.06 (9.812) | [-2.583; 1.732] |
| **End of study (V5 LOCF)** | Number of available data | 165 | 147 | -0.813 |
| | Mean (SD) | 125.25 (9.619) | 126.06 (9.871) | [-2.986; 1.361] |

The mean values of the evolution of haemoglobin values over treatment indicate the same progressive restoration of this parameter from V4 onwards in both treatment groups, thus demonstrating the effective treatment of anaemia with comparable efficacies in both treatment groups.. These results confirmed the non inferiority of V0355 compared to FERROGRAD® previously demonstrated with the primary analysis of haemoglobin levels in the PP and FAS data sets at V5.

The other secondary haematology parameters investigated were erythrocytes count, haematocrit, MCV, MCHC, platelet count, and white blood cells (WBC) count. The mean values of the evolution of these parameters over time in the PP data set indicated no statistically significant difference at any time point between the V0355 and the FERROGRAD® treatment groups. All these parameters tended to recover to values close to normal ranges, with the expected exception of WBC and platelet counts which were not affected by both treatments investigated.

Similarly, the mean values of the evolution of parameters related to iron (ferritin, transferrin, transferring saturation, soluble transferrin receptor, and iron) do not indicate any statistically significant difference at any time point between the V0355 and the FERROGRAD® treatment groups for any parameter. The evolution of iron-related parameters was nevertheless slightly slower than that of haematology parameters for both treatments.

All the symptoms of IDA, which consisted in fatigue, pallor, dyspnoea, nails disorders, loss of appetite, alteration of cognitive functions, and skin disorders improved over treatment with similar patterns in both study groups.

The evolution of the SF-12 patients' scores for physical health and for mental health did not reveal any statistically significant difference across both study groups, and all parameters showed improvements.

**Safety results**

The overall extent of exposure ranged from 3 to 134 days with a mean ± SD of 81.5 ± 25.4 days. The extent of exposure was slightly higher in the V0355 group (83.8 ± 22.2 days) than in the FERROGRAD® group (79.5 ± 28.1 days).

A total of 226 adverse events (AEs) were recorded. The number and incidence of AEs was slightly lower in the V0355 group (104 AEs in 62 patients, 31.3%) than in the FERROGRAD® group (122 AEs in 72 patients, 35.8%). Three (3) serious AEs (SAEs) were observed in 2 patients in the V0355 group and 5 SAEs were observed in 5 patients in the FERROGRAD® group. The number of AEs leading to permanent study drug discontinuation was lower in patients receiving V0355 (17 AEs in 12 patients, 6.1%) than in those who received FERROGRAD® (21 AEs in 18 patients, 9.0%). Similarly, the incidence of AEs considered related to study drug by the investigator was notably lower in the V0355 group (55 AEs in 39 patients, 19.7%) than in the FERROGRAD® group (77 AEs in 54 patients, 26.9%).

As expected for this class of drug, gastrointestinal (GI) system disorders was the most frequently affected system organ class (SOC), and was experienced by 17.7% and 21.9% of patients in the V0355 and FERROGRAD® group, respectively. The incidence of moderate and severe GI treatment-emergent AEs was significantly lower (p=0.007) in the V0355 group (11 patients, 5.6%) than in the FERROGRAD® group (28 patients, 13.9%). The other AEs were observed with comparable incidences across both study groups. Most GI AEs were of mild or moderate intensity; and the incidence of severe GI AEs was comparable in both study groups (3 patients and 1 patient in the V0355 and FERROGRAD® group, respectively).

| Name of Company: Pierre Fabre Médicament | Individual Study Table | (For National Authority Use Only) |
|---|---|---|
| Name of finished product: V0355 | Referring to Module 5 of the Dossier | |
| Name of active ingredient: Ferrous sulphate | Vol.: .....Page: ..... | |

No clinically relevant change from baseline was observed in the evolution over time of laboratory parameters investigated (reticulocytes, platelets, leukocytes, basophils, eosinophils, neutrophils, lymphocytes, monocytes, immature reticulocytes fraction, mean corpuscular volume), with the exception of mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) which both increased over time with similar patterns in both treatment groups.

No clinically relevant change from baseline was observed in the evolution over time of vital signs parameters investigated (supine systolic and diastolic blood pressure (SBP and DBP), and heart rate (HR)). The evolution pattern was similar in both study groups, without significant change in SBP (mean ± SD changes assessed at V5 of -0.7 ± 11.2 and -0.4 ± 11.5 mmHg in the V0355 and FERROGRAD® group, respectively), DBP (mean ± SD changes assessed at V5 of 0.1 ± 7.9 and -0.2 ± 8.7 mmHg in the V0355 and FERROGRAD® group, respectively), and HR (mean ± SD changes assessed at V5 of -2.9 ± 9.4 and -0.7 ± 8.6 beats per minutes in the V0355 and FERROGRAD® group, respectively).

Abnormal, not clinically relevant physical examinations were occasionally reported at various time points during the study, with comparable incidences in both study groups. The most frequently reported physical examinations were those pertaining to the gastrointestinal system, such as abdominal swelling, pain or discomfort.

Overall, 75 patients received a concomitant treatment after the start of the study medication, 35 patients (17.7%) and 40 patients (19.9%) in the V0355 and FERROGRAD® group, respectively.

**Conclusion**

In the conditions of the study, the restoration of haemoglobin level after 4, 8 and 12-weeks of administration of V0355 was not inferior to that observed with FERROGRAD®. The restoration of erythrocytes (count and %), haematocrit, haemoglobin, ferritin, mean corpuscular volume, iron, transferrin, transferrin saturation, soluble transferrin receptor, reticulocytes count and ratio soluble transferring receptors/log(ferritin) parameters showed no statistical inferiority of V0355 versus FERROGRAD®. No clinically relevant difference was observed in the number of responders between V0355 and FERROGRAD®.

Iron-deficiency anaemia (IDA) related symptoms improved over treatment, as shown by the questionnaire, without relevant difference between V0355 and FERROGRAD® treatment groups. The SF-12 survey indicated that the improvement of quality of life after 12 weeks of treatment did not differ between V0355 and FERROGRAD® treatment groups.

Both V0355 and FERROGRAD® were well tolerated, globally as well as by the gastrointestinal system after 12 weeks administration to female patients with symptomatic IDA.

No clinically significant difference between treatment groups was observed in the incidence, relationship to study drug assessed by the investigator, and intensity of SAEs and AEs leading to permanent study drug discontinuation.

The incidence of gastrointestinal AEs was statistically significantly lower (p=0.007) after administration of V0355 than after FERROGRAD®.

Haematology parameters improved over treatment, in relation to iron store in both treatments groups, without difference in the number of abnormal laboratory values between V0355 and FERROGRAD® groups. No clinically relevant change from baseline was observed in vital signs parameters.

Overall, this study demonstrated that V0355 administered at 80 mg per day exhibited an efficacy on the restoration of haemoglobin levels and iron stores, improvement of IDA-related symptoms investigated and quality of life not inferior to that of FERROGRAD® administered at 105 mg per day when during 12 weeks to female patients with symptomatic IDA. No clinically relevant differences were observed in the number of responders between V0355 and FERROGRAD® treatment groups after 4, 8 and 12 weeks of treatments.

Moreover, both drugs investigated exhibited a good tolerance, and V0355 was demonstrated to have a statistically significant better (p=0.007) tolerance than FERROGRAD® regarding moderate and severe gastrointestinal AEs, which are among the most frequent side-effects experienced by women of childbearing age suffering from iron-deficiency anaemia.

**Date of report: 26 April 2010**

**V00355 CP 301 3A – synopsis page 5/5**