STUDY SYNOPSIS

Name of Company: Vifor (International) Inc. **Name of Finished Product:** Maltofer® Fol film-coated tablets **Name of Active Ingredient:** Iron polymaltose complex
Title of Study: Comparative study of the efficacy and tolerability of iron polymaltose complex film-coated tablets with folic acid (Maltofer® Fol film-coated tablets) compared to a generic iron sulphate product in pregnant women with iron-deficiency anaemia
Protocol Number: VIT-FOLFILM-07
Study Period: **Phase of Development:** III **Date of first enrolment:** 06 Feb 2008 **Date of early study termination:** 11 Sep 2009 **Date of last completed:** 22 Oct 2009
Investigator(s): Fifty-three investigators took part in the study, most of whom were working in study centres or university hospitals and specialised in obstetrics and gynaecology.
Study Centre(s): Fifty-three centres were involved in the study (5 in Bulgaria, 3 in Estonia, 6 in Latvia, 6 in Lithuania, 7 in Romania, 3 in Switzerland, 8 in Ukraine and 15 in Russia).
Publication(s): None
Objectives: The objective of this study was the evaluation of the efficacy and tolerability of Maltofer® Fol film-coated tablets compared to a generic iron sulphate compound in iron-deficient pregnant women.
Study Design: This was a multi-centre, open-label, controlled, randomised, phase III study with 2 parallel groups. After assessment for eligibility in a 2-week screening period, pregnant women (in gestational weeks 15 to 23) with iron-deficiency anaemia were randomised to receive either Maltofer® Fol film-coated tablets (group A) or a generic iron sulphate compound (group B) twice daily for 90 days. The patients attended visits for efficacy and safety assessments at Baseline (Day 1) and Days 30, 60, and 90.
Number of Patients (planned and analyzed): It was planned to randomise 423 patients (282 to group A, 141 to group B). Overall, 961 patients were screened, and 330 patients were randomised (214 to group A and 116 to group B).
Diagnosis and Main Criteria for Inclusion: The patients fulfilled all of the following inclusion criteria: • 18 years of age and above, with iron-deficiency anaemia (haemoglobin <11.0 g/dL and ferritin ≤30 µg/L). • Mean corpuscular volume (MCV) <100 fL. • Pregnancy in gestational weeks 15 to 23. Patients were stratified according to their gestational age at inclusion in the following categories: 15 to 17, 18 to 20, and 21 to 23 weeks. • Signed informed consent. • Willingness and ability to comply with all study requirements.
Test Product, Dose and Mode of Administration, and Lot Number(s): Maltofer® Fol film-coated tablets containing iron (III)-hydroxide polymaltose complex (IPC) equivalent to 100 mg elemental iron and 400 µg folic acid were taken orally twice daily (1 tablet in the morning and 1 tablet in the evening). Patients received Maltofer® Fol film-coated tablets from batch number 6870001.
Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Plastufer® capsules containing 100 mg elemental iron plus Folsan® tablets containing 400 µg folic acid were taken orally twice daily (1 of each tablet in the morning and 1 of each tablet in the evening). Patients received Plastufer® tablets from the following batch numbers: 470 and 477. Patients received Folsan® tablets from the following batches: 40051, 43048, and 43969.
Duration of Treatment: The planned duration of treatment for each patient was about 3 months. The study was terminated early because of significant delays in patient recruitment and a change in the sponsor's business strategy. The actual mean duration of treatment was about 2.5 months in the Maltofer® Fol group and 2.9 months in the Plastufer plus Folsan group.

Name of Company:
Vifor (International) Inc.
Name of Finished Product:
Maltofer® Fol film-coated tablets
Name of Active Ingredient:
Iron polymaltose complex

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was:

- Change in haemoglobin from Baseline to end of treatment on Day 90 in both treatment groups.

The secondary efficacy endpoints were:

- Change in haemoglobin from Baseline to Day 30 and Day 60 in both treatment groups.
- Change in ferritin and transferrin saturation (TSAT) from Baseline to Days 30, 60, and 90 in both treatment groups.

Safety:

The primary safety endpoint was the number of adverse events (AEs)/reactions observed during the study period in both treatment groups.

Other safety variables included the following:

- Haematology (haematocrit [Hct], mean corpuscular haemoglobin [MCH], mean corpuscular haemoglobin concentration [MCHC], MCV), measured at every visit.
- Iron indices (serum iron, TSAT, serum ferritin) and folic acid, measured at every visit.
- Vital signs (systolic and diastolic blood pressure, pulse rate, axillary body temperature), measured at every visit.
- Body weight, measured at every visit.
  Results from physical examination, performed at screening and at Visit 4 / Early Termination Visit.

Other observational variables included:

- Concomitant medication throughout the study.
- Compliance to study medication.
- Extent of exposure.

Statistical Methods:

Because of premature termination of the study, only basic statistical safety summaries were prepared for selected variables, and no analyses or summaries of efficacy endpoints were performed. All safety summaries were based on the safety population, which comprised all patients who received at least 1 dose of study medication and were stratified by treatment group. No stratification other than by treatment group was applied.

For continuous variables, statistical summaries included the following descriptive statistics: number of observations, arithmetic mean (mean), standard deviation (SD), standard error of the mean (SEM), minimum, median, and maximum. Discrete variables were summarised in frequency tables displaying counts and percentages. All prior and concomitant medications were summarised using the World Health Organisation Drug Dictionary and AEs were coded using the Medical Dictionary for Regulatory Activities.

Name of Company:
Vifor (International) Inc.
Name of Finished Product:
Maltofer® Fol film-coated tablets
Name of Active Ingredient:
Iron polymaltose complex

Safety Results:
Mean compliance was high (99.2% overall). Mean treatment duration was approximately 2.5 months in the Maltofer® Fol group and the Plastufer plus Folsan group and total iron intake was similar between the 2 treatment groups (15.6 g in the Maltofer® Fol group and 15.3 g in the Plastufer plus Folsan group). The percentage of patients experiencing any TEAE was similar between the Maltofer® Fol group (29.0%) and the Plastufer plus Folsan group (26.1%). The incidence of severe TEAEs (2.8% of patients in the Maltofer® Fol group and 2.6% in the Plastufer plus Folsan group), and TEAEs leading to discontinuation (3.7% in the Maltofer® Fol group and 2.6% in the Plastufer plus Folsan group) was low in both treatment groups. The percentage of patients experiencing serious TEAEs was similar in the Plastufer plus Folsan group (5.2%) compared to the Maltofer® Fol group (3.7%). The percentage of patients experiencing treatment related TEAEs was similar between the Maltofer® Fol group (7.0%) and the Plastufer plus Folsan group (8.7%). No patients in either treatment group experienced serious treatment related TEAEs. No deaths occurred during the study. However, one patient (801-005) experienced serious TEAEs of premature baby and death neonatal, and one patient (903-035) experienced a serious TEAE of intra-uterine death. Both patients were receiving Maltofer® Fol.
The most common AE (by preferred term) was headache, which occurred in more patients in the Maltofer® Fol group (9.3%), compared to the Plastufer plus Folsan group (4.3%). Nausea occurred in more patients in the Plastufer plus Folsan group (5.2%) compared to the Maltofer® Fol group (1.9%).
The majority of treatment-related TEAEs were gastrointestinal disorders (6.5% of patients in the Maltofer® Fol group and 8.7% of patients in the Plastufer plus Folsan group). The majority of treatment-related TEAEs were mild or moderate in severity.
The majority of severe TEAEs, serious TEAEs and TEAEs leading to discontinuation were events in the SOC pregnancy, puerperium and perinatal conditions. The only serious TEAE reported by more than 1 patient was pre-eclampsia (3 patients [1.4%] in the Maltofer® Fol group and zero patients in the Plastufer plus Folsan group); 2 of the pre-eclampsia AEs led to treatment discontinuation. Four (1.9%) patients in the Maltofer® Fol group and 1 (0.9%) patient in the Plastufer plus Folsan group experienced severe events in the SOC pregnancy, puerperium and perinatal conditions. No individual severe serious TEAEs were reported in more than 1 patient. No other AEs leading to discontinuation were reported by more than 1 patient. Eight (3.7%) patients in the Maltofer® Fol group and 6 (5.2%) patients in the Plastufer plus Folsan group experienced TEAEs that led to hospitalisation. None of the TEAEs that led to hospitalisation were considered by the investigator to be related to study drug. The majority of the TEAEs that led to hospitalisation were either mild or moderate. Eight of the TEAEs that led to hospitalisation were severe (6 in the Maltofer® Fol group and 2 in the Plastufer plus Folsan group). The majority of TEAEs leading to hospitalisation had recovered either with or without sequelae. Patient 801-005 experienced 2 TEAEs of premature baby and death neonatal.
There were statistically significant changes from Baseline seen for all haematology and iron index parameters in both treatment groups, except for MCHC in the Maltofer® Fol group. With regards to shift from baseline, a higher percentage of patients in the Plastufer plus Folsan group compared with the Maltofer® Fol group improved from either below the normal range to within the normal range (for haematology parameters and TSAT, serum ferritin and serum iron), at the final visit.
No safety concerns were identified from the vital signs data.

Conclusions:
- Due to significant delays in patient recruitment and a change in the sponsor's business strategy, the study was terminated early. The planned efficacy analysis was cancelled and no analyses or summaries of efficacy endpoints were provided.
- The study revealed no new safety concerns in patients receiving Maltofer® Fol film-coated tablets.