2 SYNOPSIS

Name of Sponsor: Serumwerk Bernburg AG	Individual Study Table	(For National Authority use only)
Name of Finished Product: Feramyl® 50mg/ml Ampoules	Referring to Part of the Dossier Volume: Modul 3	
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Title of Study:
A single-centre, randomized, single-blind study in parallel groups to evaluate the efficacy and safety of a new intravenous iron HES preparation as compared to intravenous iron dextran (Cosmofer®) in EPO (erythropoietin) naïve patients suffering from anemia.

Investigators: Centre 1: Univ.-Prof. DDr. Walter Hörl
Centre 2: Prof. MUDr. Juraj Payer

Study Centres: Centre 1: Medical University Vienna, Dept. of Nephrology (Austria)
Centre 2: Fakultna Nemocnica s Poliklinikou Bratislava, V. Interná Klinika (Republic of Slovakia)

Studied Period: 1.2 years (from January 29th, 2010 to May 12th, 2011)

Phase of Development: IIa

Objectives:
This bridging study was planned to demonstrate clinical equivalence with respect to iron status. Primary efficacy variable is hemoglobin, secondary efficacy variables are hematocrit, transferrin saturation and serum ferritin.

To evaluate the safety and tolerability of Feramyl® as compared to the marketed study standard medication with respect to the variables vital signs (body weight, body temperature, blood pressure, heart rate) and laboratory determinations of alanine aminotransferase, aspartate aminotransferase, Gamma-GT, creatinine in serum, red and white blood count and platelets; changes in subjective well being, other subjective adverse events, changes in concomitant medications and diseases.

Methodology:
The study was formally designed as a randomized, single-blind study in parallel groups. It was the first human application of Feramyl® and was considered as a bridging study of Cosmofer® as reference product. This bridging study concept was discussed and agreed between sponsor and AGES (=Austrian CA) prior start of formal study planning. Both medications are iron preparations.

Study sensitivity was judged as verified, provided Cosmofer® yielded a statistically significant increase in average hemoglobin from baseline to day 7 visit. Day 7 data was the time point to assess equivalence. Clinical equivalence was judged as verified, provided the average hemoglobin results at day 7 are within the 0.75 to 1.33 limits as specified and justified in the study protocol and the EU guidelines (see CPMP and ICH) for testing clinical equivalence.

The efficacy and safety laboratory parameters were measured with routines of everyday practice in the centres.

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Subjective safety assessment were done by the investigators after the open question "How are you?" with a subsequent careful medical interview. Body weights to determine iron dosage were measured at the investigator's premises with a balance.

The production of the study medication was guided by GMP principles, the saline solution for infusion preparation was provided by the hospitals pharmacies. Laboratories complied with GLP standards.

Number of Subjects (planned and analysed):

A total of 50 patients - evaluable as per study protocol - was planned, based on a stratified 1:1 randomisation balanced by centre and for each study treatment group.

The fully analysed population is based on 54 patients in the intention to treat sample and on 52 in the per protocol population. Study medications are balanced in both populations from above.

Diagnosis and main in- and exclusion criteria:

Diagnosis: Anemia in patients suffering from CKD (chronic kidney disease).

Inclusion Criteria:

1. Patients suffering from anemia (females with hemoglobin in the range from 9.0-12.0 g/dl and males in the range from 9.0-13.5 g/dl).
2. Age in the range of 30-75 years, after first amendment 18-75 years, inclusive at visit 2 (baseline)
3. Patients suffering from CKD for at least six months
4. Females of child bearing potential with a safe method of contraception for the full study period
5. Patients must give written informed consent before any study specific assessment is performed.

Exclusion Criteria:

1. Females of child bearing potential without a safe method of contraception for the full study period
2. Pregnant or nursing (lactating) women
3. EPO therapy during the last three months
4. Acute or chronic intoxication
5. Inpatients of any reason, obsolete after second amendment
6. Renal failures in traumatic patients
7. Any exclusion criteria from the Cosmofer® SPC:
   anemia caused by non-iron deficiency, iron overload, disturbances in iron metabolism, excess iron, asthma, eczema, atopic allergies, rheumatoid arthritis (acute phase of SLE), severe liver disease ALT/AST > 4 time UNL, severe infections
8. Severe drug abuse
9. End stage renal disease
10. Blood transfusions during the last six months
11. HbA1c>7.5%
12. Anticipated medical need for EPO (erythropoietin) treatment during the main study period from baseline to the day 7 (visit 3) or during three months prior the baseline visit.
13. Potentially unreliable patients, and those judged by the investigator to be unsuitable for the study.

Note: Actually, all patients were outpatients. The permission to include inpatients in Vienna was set in force after IRB approval. It never materialised.

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Test product, dose and mode of administration, batch number:
Feramyl® test dosage and full dose according to the same formulae as Cosmofer®.
The manufacturer of Feramyl® was: Serumwerk Bernburg AG (SWB)
The batch numbers used in this study were: 00109 and 00110.

Duration of treatment:
One single iron dosage was infused as specified in the reference medication's SPC:
After the application of the test dose an one hour observation period for rare anaphylactic reactions was scheduled according to the Cosmofer® SPC. Thereafter - provided no adverse reaction was observed - one single full dose was applied as intravenous infusion over about four hours.

Reference therapy, dose and mode of administration, batch number:
Cosmofer®, therapy details as defined in its SPC. One single iron dosage was infused.
The manufacturer of Cosmofer® was: Gry Pharma
The batch numbers used in this study were: 00109 and 00110

Criteria for Evaluation:

Efficacy: Hemoglobin at day 7 as primary endpoint and iron status with HCT, SF, TSAT. Assessment of "assay sensitivity" for this study was defined by a required statistically significant increase of the reference therapy vs. day 1 of hemoglobin. A confidence interval based evaluation was planned and performed.

Safety: Vital signs and safety laboratory tests: RBC, WBC, platelets, serum creatinine, AST, ALT and Gamma-GT.
GCP compliant documentation of adverse and serious adverse events.

Statistical Methods

Confirmatory study for the primary endpoint based on confidence interval using Fieller's theorem, exploratory evaluation for all other study data. Alpha risk was set to the two-sided 5% level, beta risk was set to 10% (power 90%). Primary objective was to show clinical equivalence with respect to the primary endpoint.

Summary-Conclusion

Efficacy Results:
52 per protocol patients suffering from anemia in chronic kidney disease received an intravenous infusion of either Feramyl® (n=26) or Cosmofer® (n=26) and were analysed according to the study protocol. Both medications increased statistically significantly the hemoglobin levels from 11.25 (mean) +/- 0.95 (SD) at baseline to 11.61 +/- 0.92 (Feramyl®) and from 11.10 +/- 1.10 to 11.50 +/-1.23 (Cosmofer®), respectively, at day 7 after dosing. Hematocrit increased significantly in both groups. Serum ferritin and transferrin saturation showed the expected shift from iron deficiency to replenishment of iron stores.

Safety Results:

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The safety evaluation is based on 54 patients in the ITT population.
One patient (Pat# 30) with an elective eye surgery (planned before study participation) was not rated as adverse event (AE), but is listed in the AE tables for the sake of consistency with the CRFs – this patient was a Cosmofer® patient.

In 9 patient AEs were reported of which 2 were judged as serious (SAE). 5 patients with AEs including the two SAEs were observed in the Cosmofer® group. In the Feramyl® group 4 patients with AEs were observed.
SAEs: Both SAEs were observed in the Cosmofer® group: Pat# 15 was hospitalised due to urinary tract infection and urinary retention, a pre-existing condition. The patient completed the study. Pat# 53 showed an anaphylactic reaction during application of the test dose and terminated the study prematurely.
Details of all adverse events can be found in section 12 of this report.

Conclusion:
Intravenous infusion of a single dose of Feramyl® showed therapeutic equivalence with Cosmofer® in the primary endpoint hemoglobin and in the secondary endpoint hematocrit. The secondary endpoints transferrin saturation and serum ferritin did not fulfill the clinical equivalence formally; these two parameters showed at day 7 in each therapy group significant average increases vs prior infusion of the study medication. It should be noted that the Feramyl® group has a marked tendency to lower averages.
The main objective of clinical equivalence has been achieved in the primary endpoint and the first of the secondary endpoints. The secondary endpoints could be considered as clinically equivalent in our interpretation with partly relaxed criteria.
Within the context and sample size limitations of a bridging study we consider as safety summary - as a very cautious interpretation of the available data of the first human study of Feramyl® - that Feramyl® was shown to be at least as safe as Cosmofer®.

Date of report: August 2011