Synopsis

Name of Sponsor/Company: Pharmacosmos A/S	**Individual Trial Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: MonoFer®	**Volume:** NA **Page:** NA	
Name of Active Ingredient: Iron oligosaccharide		

Title of Trial:

A non-comparative open-label study of MonoFer® in patients with either chronic kidney disease or congestive heart failure with a need for parenteral iron

Investigators:

This report is an integrated report of 2 studies of MonoFer® in 2 subgroups of patients with either chronic kidney disease (CKD) or congestive heart failure (CHF).

The following investigators participated in the P-CKD-01 study (15 centres):

[redacted]

The following investigators participated in the P-CHF-01 study (9 centres):

[redacted]

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[redacted]

Trial centres:

P-CKD-01 (15 centres):

[redacted]

P-CHF-01 (9 centres):

[redacted]

Publication (reference): NA

Trial Period (years):	**Phase of Development:**
Date of first patient first visit: 31 May 2007 Date of last patient last visit: 26 August 2008	Phase III

Objectives:

The primary objective of the studies was to obtain safety reassurance with the use of MonoFer® given either as repeated IV boluses or as total dose infusion (TDI) for correction/maintenance therapy of anaemia in patients with CKD or CHF with a need for parenteral iron due to either absolute or functional iron deficiency anaemia in order to ensure that MonoFer® would not lead

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to unexpected adverse events (AEs) in these patients.

The secondary objectives were to compare haemoglobin (Hb), haematocrit (Hct), transferrin saturation (TSAT), *s*-iron, and *s*-ferritin levels 1, 2, 4, and 8 weeks after treatment start to baseline levels. In addition, the P-CHF-01 study included a linear analogue scale assessment (LASA) quality of life (QoL) questionnaire comparing QoL at baseline and 4 and 8 weeks after baseline**.**

Methodology:

The design and number of exposed patients were discussed at a scientific advice meeting with the Swedish regulatory authority, Medical Products Agency (MPA). Minutes from the scientific advice meeting is enclosed in Appendix 14.1.3.

Both studies were prospective, open-label, non-comparative, multinational, multi-centre studies.

The P-CKD-01 study was conducted at 15 centres in 3 countries; 6 centres in Denmark, 7 in Sweden, and 2 in the UK. 182 CKD patients in pre-dialysis or undergoing dialysis (either peritoneal dialysis (PD) or haemodialysis) with a need for parenteral iron due to either absolute or functional iron deficiency anaemia were included.

The P-CHF-01 study was conducted at 9 centres in 2 countries; 6 centres in Denmark and 3 in Sweden. 20 CHF patients with anaemia and a need for parenteral iron due to either absolute or functional iron deficiency anaemia were included.

A total of 6 visits were conducted during the studies. In general, the patients received MonoFer® either as 4 repeated IV boluses at visit 2, 3, 4, and 5 or as a TDI at visit 2. If the TDI exceeded 20 mg iron/kg it was split in 2 and given with 1 week interval. Laboratory assessments (haematological (Hb, leucocytes, complete blood cell count with differentials, platelets) and biochemical (sodium, potassium, creatinine, albumin, urea, bilirubin, and alanine aminotransferase (ALAT)) analyses) were performed at every visit. A complete physical examination was performed at visit 1 and 6, and vital signs and biochemical monitoring of treatment effects (Hb, Hct, TSAT, *s*-iron, and *s*-ferritin) were performed at visit 2, 3, 4, 5, and 6. In addition, the CHF patients filled in a LASA QoL questionnaire at visit 2, 5, and 6.

Number of patients (planned and analysed):

In order to obtain approximately 200 exposed patients in total it was planned to enrol 150-200 CKD patients in the P-CKD-01 study and 25-50 CHF patients in the P-CHF-01 study. In total, 202 patients were exposed to 604 treatments with MonoFer®.

In the P-CKD-01 study, 313 patients were screened, 131 were screening failures, and 182 patients were enrolled and treated with MonoFer®. In total, 584 treatments with MonoFer® were given (523 bolus injections of 100 mg MonoFer®, 17 bolus injections of 100-200 mg MonoFer®, and 44 TDIs).

In the P-CHF-01 study, 38 patients were screened, 18 were screening failures, and 20 patients were enrolled and treated with MonoFer®. All 20 patients received a TDI.

Diagnosis and main criteria for inclusion:

P-CKD-01: Patients with CKD and anaemia (Hb < 110 g/L (6.8 mmol/L) and *s*-ferritin < 800 µg/L for patient not treated with parenteral iron and Hb ≤ 130 g/L (8.1 mmol/L) and *s*-ferritin > 200 µg/L[1] but < 800 µg/L for patient in treatment with parenteral iron).

P-CHF-01: Patient with CHF and anaemia (Hb < 110 g/L[2] (6.8 mmol/L) and *s*-ferritin < 800 µg/L).

[1]After approval of a protocol amendment, the lower limit of *s*-ferritin of 200 µg/L was omitted.

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Investigational product, dose and mode of administration, batch number(s):

MonoFer® (iron oligosaccharide) given either as a fractionated IV bolus injections (slow injection rate; max 50 mg iron/min) of 100-200 mg iron at baseline and at 1, 2, and 4 weeks after baseline (visit 2, 3, 4, and 5 respectively; the last treatment may be a TDI if the total dose exceeded 800 mg) or as an IV TDI of up to 20 mg iron/kg given over 30-60 min (0-10 mg iron/kg over 30 min, 11-20 mg iron/kg over 60 min) at baseline (visit 2). If the TDI exceeded 20 mg iron/kg it was split in 2 and given with 1 week interval.

Patients may receive additional iron treatments between week 4 and 8 if their *s*-ferritin concentration was less than 300 µg/L.

The following batch numbers were used in the P-CKD-01 study: 603192A (10 ml), 745591 (10 ml), and 617291A (1 ml).

The following batch numbers were used in the P-CHF-01 study: 603192B (10 ml), 745591 (10 ml), and 617291B (1 ml).

Duration of treatment:

8 weeks.

Reference therapy, dose and mode of administration, batch number:

NA

Criteria for evaluation:

Safety (primary endpoints):

The safety endpoints for the studies were:

- AEs (number and type of AEs)
- Serious adverse events (SAEs)
- Physical examination
- Vital signs (including electrocardiogram (ECG))
- Clinical laboratory analyses (biochemistry (sodium, potassium, creatinine, albumin, urea, bilirubin, and ALAT, haematology (leucocytes, complete blood cell count with differentials, platelets))

Efficacy (secondary endpoints):

The efficacy endpoints for the studies were changes in Hb, Hct, TSAT, *s*-iron and *s*-ferritin levels 1, 2, 4, and 8 weeks after treatment start compared to baseline levels. Furthermore, a LASA QoL questionnaire was included in the P-CHF-01 study.

[2] After approval of a protocol amendment, the Hb level was raised to Hb < 115 g/L (7.1 mmol/L) in women and Hb < 120 g/L (7.4 mmol/L) in men.

Statistical Methods:

Descriptive statistics for continuous variables are presented with *N*, *N*miss, mean, standard deviation (SD), median, and min and max. *N* (*N*miss) denotes the number of patients contributing with non-missing (missing) data. For discrete variables, descriptive statistics are presented with *N* (*N*miss) and percentage of the number of patients contributing with non-missing (missing) data in the various categories of the variable where percentage was based on the total number of exposed patients which constitutes the sum of *N* and *N*miss.

In general, all safety and efficacy analyses were performed on the safety analyses set.

Safety analyses (primary analyses): The analyses for vital signs (blood pressure (BP), pulse, and weight) and laboratory data were based on descriptive statistics as described for continuous variables above. Physical examination was tabulated by body system and normal/abnormal categories as described for categorical data above. ECG data was tabulated in the same way. AEs were summary tabulated by MedDRA body system and preferred term indicating number and percentage of patients and number of events. The same tabulation was also done by severity (mild, moderate, and severe). Vital signs and laboratory data were also tabulated and summarized with values of change from baseline.

Changes in concomitant medications and medical history were only listed by patient.

Efficacy analyses: For each of the secondary endpoints (Hb, Hct, TSAT, *s*-iron, *s*-ferritin, and a QoL questionnaire (only included in the P-CHF-01 study)), the measurement at baseline was pair-wised compared to the measurement at each later visit. The endpoint values were analysed by an ANOVA regression model having visit as fixed effect. The eventual inter-correlation of the data between the visits was accounted for via an unrestricted covariance matrix. The change from baseline values was analysed via the differences of the least-square mean estimates from baseline and each of these estimates were subject to testing the null hypothesis of no difference since baseline using the associated t-test. Also, the corresponding *p*-value and 95 % CI are presented. In case of severe skewness of the data, the analyses were instead based on a non-parametric approach such as a Wilcoxon signed test and Hodges-Lehmann CI.

The change from baseline to week 4 and 8 for each of the 3 QoL questions (LASA scores) were analysed in the same way. This analysis was only included in the P-CHF-01 trial.

The analyses are supplemented with descriptive analyses as described for continuous variables above and tables displaying the results (t-test, *p*-value, CI etc.) are also presented.

Summary of results:

Safety results: In the P-CKD-01 study, a total of 244 AEs were observed. 192 events were non-serious of which 17 were probable or possible related to MonoFer® (i.e. adverse reactions). 5 of these probable or possible related events were mild, 10 were moderate, and 2 were severe. The 2 severe AEs were severe headache (patient [redacted]) and haemorrhagic cyst (patient [redacted]). The most frequent related events were gastrointestinal side effects which were observed in 6 patients (7 events). Furthermore, 52 SAEs were observed of which 2 were possible related according to the investigator and reported as suspected unexpected serious adverse reactions (SUSARs). The 2 SUSARs were sepsis with Staphylococcus aureus and unstable angina. Both events were evaluated as unlikely related to MonoFer® by the medical monitor at [redacted]

In the P-CHF-01 study, a total of 25 AEs were observed. 18 events were non-serious and 7 were SAEs. None of these were recorded as probable or possible related to MonoFer® and none were severe.

No acute anaphylactic/anaphylactoid or delayed allergic reactions were observed in either CKD or CHF patients.

Efficacy results: In the P-CKD-01 trial, all efficacy estimates (Hb, Hct, TSAT, *s*-iron, and *s*-ferritin) increased over time compared to baseline (visit 2), and most of the changes were significant. *S*-ferritin and TSAT were significantly increased at all visits. Hct was significantly increased from visit 4 to 6. Hb was not significantly changed at visit 3 and 4, but was significantly increased at visit 5 and 6. The largest difference in change from baseline in Hb was observed at visit 6 (8 weeks after baseline) with value of 3.9 g/L (0.245 mmol/L). *S*-iron was significantly increased from visit 3 to 5, but not at visit 6.

At a glance, the efficacy estimates (Hb, Hct, TSAT, *s*-iron, and *s*-ferritin) in the P-CHF-01 trial seemed to be increased to a higher extend at all visits compared to the P-CKD-01 trial. However, many of the results were non-significant probably due to the sparse amount of data.

Hb was increased at every visit compared to baseline; however, the increase was non-significant. The largest difference in change from baseline in Hb was observed at visit 4 (2 weeks after baseline) with value of 4.7 g/L (0.294 mmol/L). Hct was significantly increased at visit 6 only. TSAT and *s*-iron were significantly increased at visit 3 but not at visit 4-6. *S*-ferritin was significantly increased at all visits. All QoL assessments ("energy level", "ability to do daily activities", and "overall QoL") increased significantly at visit 5 (4 weeks after treatment). The empirical mean for "Energy level" increased by 49 %, "ability to do daily activities" increased by 38 %, and "overall QoL" increased by 23 %. At visit 6, only "energy level" was significantly increased with 34 %. "Ability to do daily activities" and "overall QoL" were increased with 20 % and 13 %, respectively, but the results were non-significant probably due to the sparse amount of data at visit 6 (8 weeks after treatment).

Conclusion:

The patient populations included reflected a naturalistic clinically relevant CKD and CHF population. They were exposed to a relevant range of iron doses and both the TDI and the bolus injections were tested. No significant unexpected safety findings were observed and MonoFer® was well tolerated in these studies. No acute anaphylactic/anaphylactoid or delayed allergic reactions were observed in either CKD or CHF patients. Iron related secondary efficacy endpoints increased as expected and were in the NICE guideline recommended interval for optimal target levels during treatment in the CKD patients. The moderate increase in Hb was expected since the majority of the patients were switched from a current parenteral iron maintenance therapy to MonoFer®. In the CHF population the clinical relevance of the relative modest Hb changes were supported by improved QoL data in the CHF population indicating that patients actually benefited from the relative modest changes in Hb.

Date of the report: 10 October 2008