2 SYNOPSIS

Serumwerk Bernburg AG	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Feramyl		
NAME OF ACTIVE INGREDIENT : Feramyl		

TITLE OF STUDY: An open label study on safety and pharmacokinetics of an intravenous administered single dose of Feramyl 200 mg in healthy blood donors compared to a single dose of Feramyl 1000mg in IBD patients to evaluate dose dependency and kinetics after 1 hour infusion.

INVESTIGATORS: Dr. Kim Krogsgaard, Principal Investigator

STUDYCENTER(S):aCROnordic Research Clinic

STUDY PERIOD: 3 Aug 13 – 29 Sep 13	**PHASE OF DEVELOPMENT: I/II**

OBJECTIVES:

- To evaluate the dose dependency of Feramyl 200 mg vs. Feramyl 1000 mg administered over 1 hour intravenously with respect to Cmax, Tmax and AUC,
- To evaluate the safety of 1-hour infusion time by monitoring of vital signs and clinical chemical safety parameters,
- To evaluate the Cmax, Tmax, AUC, half-life, elimination constant, volumes of distribution and urine excretion compared to literature data for competitors and
- To evaluate standard clinical chemistry safety parameters and compare the results after 200 mg to 1000 mg and compare literature data for competitors

METHODOLOGY: Healthy volunteers were recruited among blood donors, who had donated at least 400 ml within the last 2 weeks. Patients with inflammatory bowel disease with anaemia and iron deficiency documented by levels of haemoglobin and serum

ferritin as well as serum transferrin saturation were planned to be recruited from three different departments of gastroenterology and by advertising.
NUMBER OF SUBJECTS (PLANNED AND ANALYZED): A total of 15 healthy blood donors were recruited to the group where 200 mg Feramyl dose was administered. One subject was never dosed, 14 subjects were dosed of whom 8 were fully evaluable and included in the PK analysis. It turned out to be impossible to recruit patients with Inflammatory Bowel disease (IBD) who fulfilled the inclusion exclusion criteria in the 1000mg Feramyl dosing group. Thus no subjects were included and dosed in this group.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy volunteers should have donated a minimum of 400 ml of blood within two weeks before dosing and IBD patients should have anaemia defined as Hgb level below 12 g/100ml (women) and 13 g/100ml (men), with ferritin < 30 µg/L and TSAT < 30 %.
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER: Group I: Feramyl 200 mg diluted in 100 ml 0.9 % NaCl given in 60 minutes. Group II: Feramyl 1000 mg diluted in 250 ml 0.9 % NaCl given in 60 minutes.
DURATION OF TREATMENT: Single dose infusion IV of 60 min
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER: NA
CRITERIA FOR EVALUATION: Dose normalized C_{max}, and AUC and $t_{½}$ after 200mg/1000 mg. **EFFICACY:**Dose normalized Cmax and AUC and t½ **SAFETY:** Standard clinical chemistry parameters and blood pressure and heart rate BP/HR hourly for 8 hours and after 24 hours post dosing as well as, adverse events and vital signs.
PHARMACOKINETIC ANALYSIS: Sugar bound serum iron levels as change from baseline iron value were to be analyzed for each subject by a standard no compartmental pharmacokinetic analysis (WinNonlin V5.3).

The calculated dose normalized Cmax and AUC and half-life were to be compared between the two subject groups by bioequivalence analysis and unpaired t-test. However, this was not possible as subjects were not included in the 1000 mg group

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

- The half-life of Fe not bound to transferrin was rather short (1.65±0.60 h) indicating a rapid cellular uptake of sugar bound Fe.
- The half-life of Fe not bound to transferrin is considerably lower as compared to literature data for competitor compounds
- Fe in urine was below the level of detection in all subjects which suggests a high stability of Feramyl in plasma.
- The absence of Fe in urine suggest a renal excretion which is even lower than that reported for competitor compounds, which supports a very stable iron sugar complex for Feramyl.
- A rise in transferrin bound iron was found, which indicates clinical efficacy, as iron must have been subject to cellular extraction from the complex and transfer to plasma for erythropoiesis.

SAFETY RESULTS:

- A total of five adverse events were recorded during the study.
- Four adverse events were mild in nature and resolved and were all assessed to be unlikely related to the study drug.
- One adverse event (elevated AST) occurred after drug administration the AST rise was just above upper normal limit and of no clinical relevance.

CONCLUSION: The dose of 200 mg Feramyl was well tolerated. A low half-life and absence of measurable renal excretion suggest that the transfer of iron to transferrin is very quick. No subject experienced a severe adverse event.

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