Clinical trial results:
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 1000 mg in IBD patients to evaluate dose dependency and kinetics after 1 hour infusion.

Summary

EudraCT number	2013-001123-39
Trial protocol	DK
Global end of trial date	29 September 2013

Results information

Result version number	v1 (current)
This version publication date	15 May 2016
First version publication date	15 May 2016
Summary attachment (see zip file)	Synopsis SWB0113 (Synopsis SWB0113.pdf)

Trial information

Trial identification

Sponsor protocol code	SWB0113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Serumwerk Bernburg AG
Sponsor organisation address	Hallesche Landstrasse 105b, Bernburg, Germany, 06406
Public contact	Susanne Manhart, Serumwerk Bernburg, +49 3471860180, smanhart@serumwerk.de
Scientific contact	Susanne Manhart, Serumwerk Bernburg, +49 3471860180, smanhart@serumwerk.de
Sponsor organisation name	Serumwerk Bernburg AG
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2013
Global end of trial reached?	Yes
Global end of trial date	29 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The protocol was approved by local ethics committee and competent authority. The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. Informed consent was obtained in writing prior to any trial-related activities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened in the period June 2013 to September 2013. The trial took place at one site in Denmark.

Pre-assignment

Screening details:

Healthy blood donors, who have donated at least 400 ml blood within the last 2 weeks. Age between 18–45 years and who were willing to provide written informed consent were considered eligible to participate in the trial.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Healthy blood donors

Arm description:

Healthy blood donors, who had donated at least 400 ml within the last two weeks, Feramyl 200 mg diluted in 100 ml 0.9% NaCL solution, administered intravenously in 60 minutes

Arm type	Experimental
Investigational medicinal product name	Feramyl
Investigational medicinal product code	
Other name	iron HES
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

single dose, intraveneous infusion over 60 min

Number of subjects in period 1	Healthy blood donors
Started	15
Completed	8
Not completed	7
not able to get stable iv access	1
blood samples lost	6

Baseline characteristics

Reporting groups

Reporting group title	Healthy blood donors

Reporting group description:

Healthy blood donors, who had donated at least 400 ml within the last two weeks, Feramyl 200 mg diluted in 100 ml 0.9% NaCL solution, administered intravenously in 60 minutes

Reporting group values	Healthy blood donors	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Adults (18-64 years)	15	15	
Age continuous Units: years arithmetic mean standard deviation	 29.58 ± 4.7	 -	
Gender categorical Units: Subjects			
Female	7	7	
Male	8	8	

Subject analysis sets

Subject analysis set title	PK/Efficacy
Subject analysis set type	Per protocol

Subject analysis set description:

Fourteen subjects were dosed and were available for the safety analysis. Samples from six patients were not analyzed for pharmacokinetic analysis since their blood samples were accidentally destroyed. Hence eight subjects completed the study and were available for pharmacokinetic analysis

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Fourteen subjects were dosed and were available for the safety analysis.

Reporting group values	PK/Efficacy	Safety	
Number of subjects	8	14	
Age categorical Units: Subjects			
Adults (18-64 years)	8	14	
Age continuous Units: years arithmetic mean standard deviation	 29.59 ± 4.17	 29.39 ± 4.64	
Gender categorical Units: Subjects			
Female	5	7	
Male	3	7	

End points

End points reporting groups

Reporting group title	Healthy blood donors

Reporting group description:

Healthy blood donors, who had donated at least 400 ml within the last two weeks, Feramyl 200 mg diluted in 100 ml 0.9% NaCL solution, administered intravenously in 60 minutes

Subject analysis set title	PK/Efficacy
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Subject analysis set description:

Fourteen subjects were dosed and were available for the safety analysis. Samples from six patients were not analyzed for pharmacokinetic analysis since their blood samples were accidentally destroyed. Hence eight subjects completed the study and were available for pharmacokinetic analysis

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Fourteen subjects were dosed and were available for the safety analysis.

Primary: dose-dependency cmax, tmax, AUC

End point title	dose-dependency cmax, tmax, AUC[1]

End point description:

The primary efficacy endpoint was 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. The primary efficacy endpoint could not be addressed because no subject was dosed with Feramyl 1000 mg. This in turn was because none of the IBD anaemia patients were recruited in the group as it proved difficult due to the inclusion and the exclusion criteria.

End point type	Primary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Blood sampling time Points (h): -0.25, 0.01, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 24.00, 168.00

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary efficacy endpoint was 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. The primary efficacy endpoint could not be addressed because no subject was dosed with Feramyl 1000 mg. This in turn was because none of the IBD anaemia patients were recruited in the group as it proved difficult due to the inclusion and the exclusion criteria.

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[2]			
Units: yes/No				
dose-dependency	0			

Notes:

[2] - The primary efficacy endpoint could not be addressed because no subject was dosed with Feramyl 1000

Statistical analyses

No statistical analyses for this end point

Primary: safety of a1-hour infusion

End point title	safety of a1-hour infusion[3]

End point description:

The primary safety endpoint was to evaluate the safety of a1-hour infusion time by monitoring vital signs, clinical chemical safety parameters and adverse events.

End point type	Primary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: for incidence of AEs and SAEs no statistical analysis was done also because of small number of cases

End point values	Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	14[4]			
Units: incidence of AEs/SAEs				
incidence of AEs	5			
incidence of SAEs	0			

Notes:

[4] - 5 adverse events in 3 subjects, all mild in nature and unlikely related to study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax

End point title	Cmax

End point description:

The secondary efficacy endpoints were to evaluate the Cmax, Tmax, AUC, half life, elimination constants, volumes of distribution and urine excretion compared to literature data for competitors.Cmax, the maximum observed serum concentration. Non-compartmental PK Analysis. The coefficient of determination, R2, for λz has to be >0.85 otherwise estimates of AUC, t½, Vz, and CL are not acceptable. AUC%Extrap should preferably not exceed 25 % in order not to reduce precision of AUC, Vz and CL.

End point type	Secondary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Blood sampling time Points (h): -0.25, 0.01, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 24.00, 168.00

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: mg/ml				
arithmetic mean (standard deviation)				
Cmax	44.3 (± 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: tmax

End point title	tmax

End point description:

The secondary efficacy endpoints were to evaluate the Cmax, Tmax, AUC, half life, elimination constants, volumes of distribution and urine excretion compared to literature data for competitors. tmax, time for occurrence of Cmax. Non-compartmental PK analysis. The coefficient of determination, R2, for λz has to be >0.85 otherwise estimates of AUC, t½, Vz, and CL are not acceptable. AUC%Extrap should preferably not exceed 25 % in order not to reduce precision of AUC, Vz and CL.

End point type	Secondary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Blood sampling time Points (h): -0.25, 0.01, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 24.00, 168.00

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: hr				
arithmetic mean (standard deviation)				
tmax	1.18 (± 0.376)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-t)

End point title	AUC (0-t)

End point description:

The secondary efficacy endpoints were to evaluate the Cmax, Tmax, AUC, half life, elimination constants, volumes of distribution and urine excretion compared to literature data for competitors. AUC(0-t), the area under the serum concentration curve from zero until the last concentration, Cz, calculated from the linear trapezoidal rule. Non-compartmental PK analysis. The coefficient of determination, R2, for λz has to be >0.85 otherwise estimates of AUC, t½, Vz, and CL are not acceptable. AUC%Extrap should preferably not exceed 25 % in order not to reduce precision of AUC, Vz and CL.

End point type	Secondary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Blood sampling time Points (h): -0.25, 0.01, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 24.00, 168.00

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: h*mg/l				
arithmetic mean (standard deviation)				
AUC	141.8 (± 42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lambda z

End point title	Lambda z

End point description:

The secondary efficacy endpoints were to evaluate the Cmax, Tmax, AUC, half-life, elimination constants, volumes of distribution and urine excretion compared to literature data for competitors.
λz, the terminal slope of the serum concentration curve in a semi-logarithmic plot used for calculation of t½, the terminal half-life. Non-compartmental PK analysis. The coefficient of determination, R2, for λz has to be >0.85 otherwise estimates of AUC, t½, Vz, and CL are not acceptable. AUC%Extrap should preferably not exceed 25 % in order not to reduce precision of AUC, Vz and CL.

End point type	Secondary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Blood sampling time Points (h): -0.25, 0.01, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 24.00, 168.00

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: 1/h				
arithmetic mean (standard deviation)				
Lambda z	0.453 (± 0.107)			

Statistical analyses

No statistical analyses for this end point

Secondary: half-life

End point title	half-life

End point description:

The secondary efficacy endpoints were to evaluate the Cmax, Tmax, AUC, half life, elimination constants, volumes of distribution and urine excretion compared to literature data for competitors. t½, the terminal half-life. Non-compartmental PK analysis. The coefficient of determination, R2, for λz has to be >0.85 otherwise estimates of AUC, t½, Vz, and CL are not acceptable. AUC%Extrap should preferably not exceed 25 % in order not to reduce precision of AUC, Vz and CL.

End point type	Secondary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Blood sampling time Points (h): -0.25, 0.01, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 24.00, 168.00

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: hr				
arithmetic mean (standard deviation)				
t1/2	1.65 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: volume of distribution

End point title	volume of distribution

End point description:

The secondary efficacy endpoints were to evaluate the Cmax, Tmax, AUC, half life, elimination constants, volumes of distribution and urine excretion compared to literature data for competitors. Vz,the apparent volume of distribution during the terminal phase. Non-compartmental PK analysis. The coefficient of determination, R2, for λz has to be >0.85 otherwise estimates of AUC, t½, Vz, and CL are not acceptable. AUC%Extrap should preferably not exceed 25 % in order not to reduce precision of AUC, Vz and CL.

End point type	Secondary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Blood sampling time Points (h): -0.25, 0.01, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 24.00, 168.00

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: l/kg				
arithmetic mean (standard deviation)				
Vz	0.046 (± 0.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: iron urine exretion

End point title	iron urine exretion

End point description:

The secondary efficacy endpoints were to evaluate the Cmax, Tmax, AUC, half life, elimination constants, volumes of distribution and urine excretion compared to literature data for competitors.
Fe in Urine was below Limit of qualification in all subjects.

End point type	Secondary

End point timeframe:

Enrollment period: Visit 1 (-1 week)
Treatment period: Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 7)
Urine sampling period: -2 - 0 hours pre-dose, 0 - 8 hours post-dose, 8 - 24 hours post-dose

End point values	PK/Efficacy			
Subject group type	Subject analysis set			
Number of subjects analysed	8[5]			
Units: mg/ml				
arithmetic mean (standard deviation)				
Fe urine	0 (± 0)			

Notes:

[5] - Fe in urine was below limit of quantification

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the time a subject had signed the ICF and until he/she has completed the study, all AEs/SAEs were collected in the CRF.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Healthy blood donors
Reporting group description:	
Healthy blood donors received 200 mg Feramyl diluted in 100 ml Saline solution as intravenous Infusion within 1 hour.	

Serious adverse events	Healthy blood donors		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Healthy blood donors		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 14 (21.43%)		
General disorders and administration site conditions			
Dysphagia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tired			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
arm pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Discomfort subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Hepatobiliary disorders Elevated AST subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The primary efficacy endpoint could not be addressed because no subject was dosed with Feramyl 1000 mg. This in turn was because none of the IBD anaemia patients were recruited in the group as it proved difficult due to the inclusion and the exclusio

Notes: