Official Title: **Multicenter, Open-label Active-controlled Randomized Study of Efficacy and Safety of Ferrum Lek® (Iron (III) Hydroxide Polymaltosate), 100 mg Chewable Tablets (Lek d.d., Slovenia) Compared With Maltofer® (Iron (III) Hydroxide Polymaltosate), 100 mg Chewable Tablets (Vifor S.A., Switzerland), in Treatment of Patients With Mild and Moderate Iron-deficiency Anaemia**

NCT Number: NCT03993288

Document Date: Statistical Analysis Plan Version 1.0: 06 April 2020

/Logotype: Research/

STATISTICAL ANALYSIS PLAN

Statistical Analysis Plan

Sponsor	Sandoz CJSC
Protocol title	A multicenter, open-label, randomized, active-controlled study to evaluate the efficacy and safety of Ferrum Lek® (iron (III) hydroxide polymaltosate), 100 mg chewable tablets (Lek d.d., Slovenia), as compared to Maltofer® (iron (III) hydroxide polymaltosate), 100 mg chewable tablets (Vifor S.A., Switzerland), in subjects with mild and moderate iron deficiency anemia
Protocol No.	TE_005_FER_CHT

Author	[redacted]
Statistical Analysis Plan version	**1.0**
Date of version	**April 6, 2020**

/Logotype: Research/

STATISTICAL ANALYSIS PLAN

Approved by

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Document history

Version	Reason for change	Date
1.0	Original document	April 6, 2020

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List of abbreviations and definitions of terms

ANOVA	Analysis of variance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HFE	Hemochromatosis gene
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ITT	Intention-to-treat
LD100	Lethal dose, the average dose of the substance in milligrams per kilogram of live weight, which causes the death of 100% of experimental animals
LD50	Half-lethal dose, the average dose of the substance in milligrams per kilogram of live weight, which causes the death of 50% of experimental animals
MLE	Maximum likelihood estimation
PP	Per protocol
BP	Blood pressure
ALT	Alanine aminotransferase
JSC	Joint-stock company
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
VAS	Visual analog scale
HIV	Human immunodeficiency virus
IUS	Intrauterine system
IUD	Intrauterine device
Hb	Hemoglobin
GOST	State standard
GOSTR	State Standard of Russia
DBP	Diastolic blood pressure
ID	Iron deficiency
CI	Confidence interval
DMPO	5,5-Dimethyl-1-pyrroline-N-oxide
IDA	Iron-deficiency anemia
GI	Gastrointestinal
GI tract	Gastrointestinal tract

CRF	Case record form
CRO	Contract research organization
LDL	Low-density lipoprotein
MoH	Ministry of health
MIC	Minimum inhibitory concentration
ICD	International Classification of Diseases
GCP	Good Clinical Practice
IEC	Independent ethics committee
AE	Adverse event
SmPC	Summary of Product Characteristics
PVC	Polyvinyl chloride
IHPC	Iron (III) hydroxide polymaltose complex
IPC	Iron polymaltose complex
PND	Postnatal days
PCR	Polymerase chain reaction
RMSAH/ RSC	The Russian Medical Society on Arterial Hypertension/ The Russian Society of Cardiology
ITP	Iron transport proteins 1 and 2
RE	Reticuloendothelial (cells)
RES	Reticuloendothelial system
SBP	Systolic blood pressure
SAE	Serious adverse event
SOD	Superoxide dismutase
SOP	Standard operating procedure
TF	Transferrin
TfR	Transferrin receptor
FL	Federal law
Full name	First name, Patronymic, Last name
CNS	Central nervous system
Cp	Ceruloplasmin
RR	Respiration rate
HR	Heart rate
ECG	Electrocardiography

1. Introduction

This study is planned and carried out to demonstrate the non-inferiority and safety of Ferrum Lek® (iron (III) hydroxide polymaltosate), 100 mg chewable tablets (Lek d.d., Slovenia), compared to MALTOFER® (Vifor S.A., Switzerland), in subjects with mild and moderate iron deficiency anemia.

The objective of this Statistical Analysis Plan is more detailed, compared to Section 9 of the study protocol, description of the main principles of the protocol-based statistical analysis, description of the primary and secondary endpoints analysis methods as well as other data obtained during the study.

This Plan stipulates for conformance of the scheduled and conducted statistical analysis to the study protocol, including the definition of the analysis data sets, transformations and calculations for the endpoints, observations quantity needed, etc.

2. Study objectives and design

2.1. Study objectives

2.1.1. Primary objective

To demonstrate non-inferior therapeutic efficacy of Ferrum Lek® by evaluating its effect on blood hemoglobin levels (g/L) when taken as 2 tablets (200 mg) per day for 12 weeks in subjects with mild to moderate iron deficiency anemia versus 2 tablets (200 mg) per day of MALTOFER® administered over the same period.

2.1.2. Secondary objectives

To evaluate the safety of Ferrum Lek® with 2 tablets (200 mg) per day versus MALTOFER® with 2 tablets (200 mg) per day by evaluating the rates, characteristics, severity of AEs, and their relation to the prescribed treatment.

2.2. Study design

This study is a multicenter, randomized, open-label, prospective, comparative, phase III, parallel-group, active control study conducted in the Russian Federation.

The eligible and ineligible subjects will be randomized into two treatment groups at the ratio of 1:1.

The subjects in the first group (168 subjects) will receive 2 tablets daily (200 mg) of Ferrum Lek® chewable tablets, during or right after meals; the daily dose should be administered once daily (as a single dose). The subjects in the second group (168 subjects) will receive 2 tablets daily (200 mg) of MALTOFER® chewable tablets, during or right after meals; the daily dose should be administered once daily. Subjects will take the medicinal products daily for 12 weeks and fill out a diary (see Appendix 17.1), where they will register administration of the study medicinal products and concomitant therapy.

All subjects will undergo a complete blood count and blood biochemistry. Therapy under investigation also includes an interim Visit 2 (Day 29 ± 2), Visit 3 (Day 57 ± 2), and final Visit 4 (84 ± 2). After the final visit, a subject's participation in the study shall be terminated, and further treatment shall be performed by a consulting physician.

The study design is depicted in Figure 1.

4.2.6. Study design flowchart

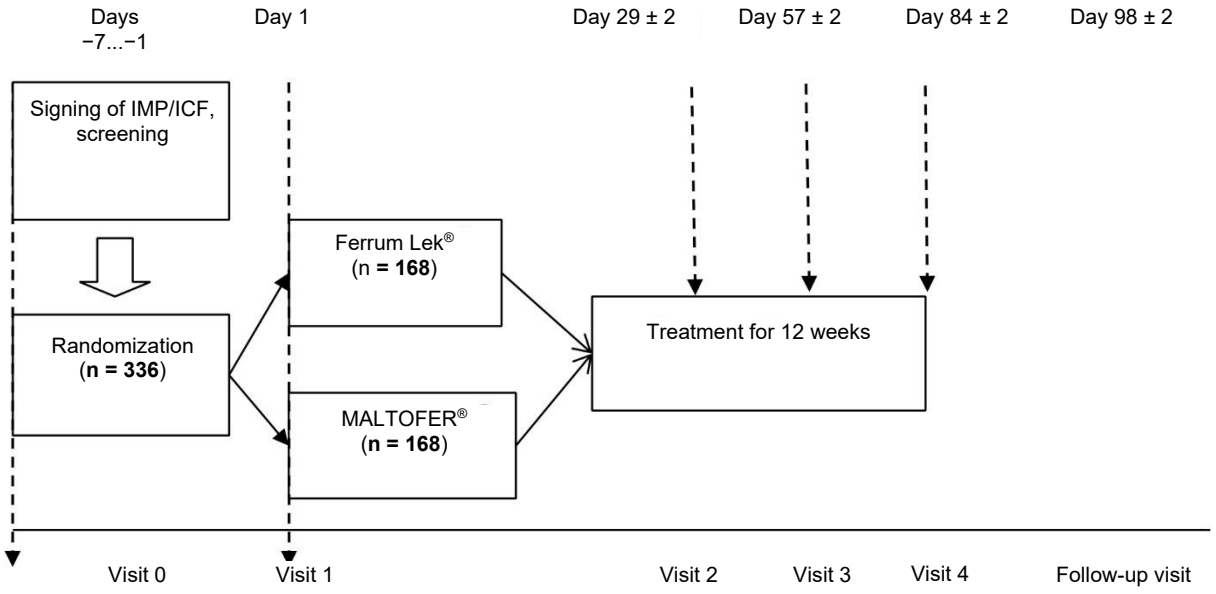

Figure 1. Study design flowchart

Study duration

The total duration of the study will be no more than 12 months, including enrollment (9 months), treatment (3 months), and follow-up (by phone) 14 days after the completion of the active treatment period.

Description of visits

4.2.9.1. Visit 0 (screening, days −7...−1)

Visit objectives:

- Signing of the informed consent;
- Assessment of the inclusion/exclusion criteria;

- Collection of demographic and anthropometric data;
- Collection of medical history data on iron deficiency anemia and significant concomitant diseases;
- Physical examination, blood pressure and heart rate measurement;
- Laboratory tests:
    - Urinalysis [general properties (color, pH, specific gravity, protein) and sediment microscopy];
    - Urine pregnancy test;
    - HIV antibody test, except for subjects who had an HIV test within the last 6 months;
    - Blood biochemistry (total protein, total and conjugated bilirubin, AST, ALT, alkaline phosphatase, creatinine, glucose, CRP);
    - Complete blood count (hemoglobin level, hematocrit, RBC, PLT, WBC, leucogram, ESR);
    - Metabolic parameters of iron (serum ferritin and iron level, transferrin, iron transferrin saturation percentage);
    - Determining blood vitamin B9 (folic acid) and vitamin B12 (cyanocobalamin) levels;
    - Determining blood TSH and T4 levels;
    - Creatinine clearance calculation according to the Cockroft-Gault formula;
- Evaluation of the concomitant therapy; • Adverse events registration.

4.2.9.2. Visit 1 (randomization/ start of the treatment, Day 1)

Visit objectives:

- Assessment of the inclusion/exclusion criteria;
- Randomization;
- Start of the treatment with the investigational medicinal product;
- Hand-out of the patient diary (Appendix 17.1) and instructions on its completion;
- Accounting and dispensing of the investigational medicinal product;
- Evaluation of the concomitant therapy; • Adverse events registration.

4.2.9.3. Visit 2 (continuation of the treatment, Day 29 ± 2)

Visit objectives:

- Physical examination, blood pressure and heart rate measurement;

- Metabolic parameters of iron (serum ferritin and iron level, transferrin, iron transferrin saturation percentage);
- Complete blood count (hemoglobin level, hematocrit, RBC);
- Hand-out of the patient diary (Appendix 17.1) and instructions on its completion;
- Check of a patient diary completion and collection of diaries;
- Accounting and dispensing of the investigational medicinal product;
- Evaluation of compliance;
- Evaluation of the concomitant therapy;
- Adverse events registration.

4.2.9.4. Visit 3 (continuation of the treatment, Day 57 ± 2)

Visit objectives:

- Physical examination, blood pressure and heart rate measurement;
- Metabolic parameters of iron (serum ferritin and iron level, transferrin, iron transferrin saturation percentage);
- Complete blood count (hemoglobin level, hematocrit, RBC);
- Hand-out of the patient diary (Appendix 17.1) and instructions on its completion;
- Check of a patient diary completion and collection of diaries;
- Accounting and dispensing of the investigational medicinal product;
- Evaluation of compliance;
- Evaluation of the concomitant therapy;
- Adverse events registration.

4.2.9.5. Visit 4 (efficacy and safety assessment, Day 84 ± 2)

Visit objectives:

- Physical examination, blood pressure and heart rate measurement;
- Laboratory tests:
    - Urinalysis [general properties (color, pH, specific gravity, protein) and sediment microscopy];
    - Urine pregnancy test;

- Blood biochemistry (total protein, total and conjugated bilirubin, AST, ALT, alkaline phosphatase, creatinine, glucose, CRP);
- Complete blood count (hemoglobin level, hematocrit, RBC);
- Metabolic parameters of iron (serum ferritin and iron level, transferrin, iron transferrin saturation percentage).

- Check of a patient diary completion and collection of diaries;
- Accounting and dispensing of the investigational medicinal product;
- Evaluation of compliance;
- Evaluation of the concomitant therapy;
- Adverse events registration.

4.2.9.6. Follow-up visit (Visit 5, Day 98 ± 2)

A follow-up visit shall be conducted by phone to find out about the patient's state and any AEs. It will be conducted 14 days after the completion of treatment.

Follow-up visit procedures (by phone):

- Evaluation of adverse events.

In case of adverse events, the patient might be invited to visit the study site.

2.3. Sample size

The sample size was calculated on the basis of the published articles, where the efficacy of iron (III) hydroxide polymaltosate was studied:

1) Maltofer, Product Information http://www.aspenpharma.com.au/product_info/pi/PI_Maltofer.pdf
2) Santiago P. Ferrous versus ferric oral iron formulations for the treatment of iron deficiency: a clinical overview. Scientific World Journal. 2012;2012:846824.
3) Geisser P. Safety and efficacy of iron(III)-hydroxide polymaltose complex / a review of over 25 years' experience. Arzneimittelforschung. 2007;57(6A):439-52;
4) Toblli JE, Brignoli R. Iron(III)-hydroxide polymaltose complex in iron deficiency anemia/ review and meta-analysis. Arzneimittelforschung. 2007;57(6A):431-8);
5) Reinisch W, Staun M, Tandon RK, Altorjay I, Thillainayagam AV, Gratzer C, Nijhawan S, Thomsen LL. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED). Am J Gastroenterol. 2013 Dec;108(12):1877-88.

6) Zaim M, Piselli L, Fioravanti P, Kanony-Truc C. Efficacy and tolerability of a prolonged release ferrous sulphate formulation in iron deficiency anaemia: a non-inferiority controlled trial. Eur J Nutr. 2012 Mar;51(2):221-9.

Based on these publications, the hemoglobin levels increased by an average of 8–15 g/L, with SD of up to 15 g/L, following 12 weeks of oral administration of iron (III) hydroxide polymaltosate complex preparations. Since approximately the same efficiency is assumed in both groups, a zero difference in the main efficiency parameter will be used to calculate the sample size. In order to take into account the maximum variability of the primary endpoint variable for the study with sufficient statistical power, the maximum standard deviation value of 15 g/L was used.

The value of 5 g/L was chosen as the non-inferiority cut-off (in accordance with the limit established and justified in the above publications).

Thus, the following assumptions were proposed for calculations:

1) It is assumed that changes in the hemoglobin level in the blood (g/L) after 12 weeks of iron deficiency anemia therapy (at the final visit) compared to the initial value (at Screening Visit 0) will be approximately the same in the group receiving the investigational medicinal product and in the group receiving the reference product (i.e., the expected difference between the two groups will be zero).
2) A pooled standard deviation for the changes in hemoglobin levels was 15 g/L.
3) The non-inferiority margin is 5 g/L.
4) The significance level (two-sided, according to the recommendations by the Food and Drug Administration) is 95%, which corresponds to a one-sided type I error of 0.05.
5) The study power is 80%, which corresponds to a type II error of 0.20.
6) Statistical hypotheses are the demonstration of non-inferiority:

$$H0: \mu A - \mu B \leq 5.0 \qquad H1: \mu A - \mu B > 5.0$$

7) The ratio between the test and control group sizes is 1:1.
8) The interim analysis will be conducted when 70% of the total sample size is reached.
9) The O'Brian-Fleming alpha-spending function will be applied with 80% power for the efficiency frontier, which will satisfy the following critical values of the t-test: 2.628 for the intermediate analysis (corresponding to $p = 0.005$) and 1.976 for the final analysis (corresponding to $p = 0.0245$).

Calculations were performed using the clinfun package of the R software, in which the calculation of a fixed sample size for interim and final analyses was performed using the group sequential design.

According to the data obtained with the clinfun package, 143 subjects in each group (total: 286 subjects) should complete the study to confirm the hypothesis of non-inferiority. For the interim analysis, data for 200 subjects (100 in each group) that are suitable for analysis should be obtained. Taking into account the frequency of premature discontinuation of the study, which is 15%, it is necessary to randomize 336 people (168 people in each group). Taking into consideration the withdrawal rate based on the results of the screening that equals to 30%, about 480 people should undergo screening to achieve the target level of randomization.

3. General analysis values

3.1. General assumptions and baseline conditions

Clinical and statistical significance

All the statistical tests within this study will be performed at a 95% confidence level (threshold value p to confirm statistical significance is 0.05).

3.2. Processing missing data

A method of filling in the missing data based on maximum likelihood estimation (MLE) for the primary endpoint will be applied if needed.

The analysis of the rest of endpoint types and other parameters will be performed only on the basis of the available information without filling in the missing data in view of the short duration of the clinical study.

4. Study participants

4.1. Patient distribution

Upon signing of the informed consent for participation in the study, the subjects undergo screening for up to 7 days. The eligible and ineligible subjects will be randomized into two treatment groups at the ratio of 1:1.

Automated randomization sheets will be generated; randomization will be carried out through an electronic CRF system with a randomization module.

Each randomized patient will receive a unique number for the medicinal product dispensing during the study. The patient's number contains R letter and numbers from 001 to 336. Patients numbering does not depend on the study site and is consecutive. In addition to the number, the system will indicate the treatment group to which the patient is randomized. Randomization will be stratified according to two factors: 1) Sex (men vs. women); 2) Hemoglobin level (80–94 g/L versus 95–110 g/L). The randomization number cannot be changed during the study.

The medicinal product is given to the patient according to the information about the treatment group received from the CRF system. Study treatment also cannot be changed in the process of the study.

Serious deviations from the Protocol should be reported as soon as possible to the Sponsor by the site staff and/or CRO and Monitor (if they are at the Site).

The Sponsor must be informed of minor protocol deviations within 10 business days but before the start of the next study period or before the start of the bioanalytical/statistical phase.

Sponsor has the right to terminate the study, and the Investigator has the right to stop subjects recruitment at any time. In the case of premature closing of the center/study, all completed as well as unused CRFs (including unused pages of partially completed CRFs) and other documents (excluding documents that must be kept in the center) must be returned to the Sponsor. Study materials can be destroyed only with the consent of the Sponsor.

4.3. Study population

4.3.1. Safety population

All randomized subjects who received at least one dose of the investigational medicinal product and completed at least one safety parameters evaluation visit. As distinct from ITT population, the TS population will be analyzed depending on actually received treatment (not only prescribed) (in case of difference between the prescribed and received therapies).

4.3.2. ITT population receiving treatment

All randomized subjects who received at least one dose of the investigational medicinal product and completed at least one efficacy parameters evaluation visit.

4.3.3. Per protocol set

All randomized subjects who completed participation in the study in accordance with the protocol (have completed the prescribed period of treatment and follow-up without significant deviations from the protocol).

5. Demographics and baseline characteristics

All the data obtained in the groups before the study therapy initiation (demographic, laboratory, instrumental, and physical examinations data, vital signs, etc.) will be compared between the groups to determine the groups' comparability for analysis.

The Fisher's exact test and χ^2 (chi-square) will be used to compare the qualitative and serial data, while the t-test or the Mann–Whitney test will be used for the quantitative data (depending on the quantitative data distribution).

To assess the normality of the distribution, the Shapiro-Wilk test will be applied. In the event that any of the initial data reveal the incomparability of the study groups (statistically significant differences in demographic and other initial data between the groups), the analysis of the efficacy and safety parameters will be additionally performed, together with the primary planned analysis, using multi-factor statistics (ANOVA, ANCOVA, or logistic regression analysis depending on the type of the studied parameter), as adjusted for the initial indicator(s) that vary between the groups.

6. Concomitant therapy

6.1. Permitted concomitant therapy

Patients will take medications, which they took before the enrollment, for the treatment of concomitant diseases during the study. Women that take oral contraceptives may continue taking them during the study.

It is permitted and recommended to take vitamins (not containing iron), folic acid, and ascorbic acid by medical prescription as well as adhere to a diet with products rich in iron.

It is not recommended to take non-steroidal anti-inflammatory medicinal products groundlessly, including selective inhibitors of cyclooxygenase, but these medicinal products may be prescribed by the Investigator due to medical indications.

6.2. Prohibited concomitant therapy

During the study, the enrolled patients must not take the following products:

- prescribed for iron deficiency anemia:

Pharmacotherapeutic groups	**Active substance (INN)**
Vitamin and mineral supplements	
Macro- and microelement supplements	
Vitamins and pseudovitamins	Ascorbic acid

	Pyridoxine
	Riboflavin
Vitamin and pseudovitamins in combinations	Multivitamins + Minerals
Macro- and microelements	Iron protein succinylate
	Hematogen
Macro- and microelements in combinations	Ferrous sulfate + Serine + Folic acid
	Multivitamins + Minerals
Hematopoiesis-stimulating agents	Iron (III) hydroxide polymaltosate complex
	Iron (III) hydroxide sucrose complex
	Ferrous gluconate
	Ferric carboxymaltosate
	Iron protein succinylate
	Ferrous sulfate
	Ferrous fumarate
	Ferrous chloride
	Cyanocobalamin
Hematopoiesis-stimulating agents in combinations	Iron (III) hydroxide polymaltosate complex + Folic acid
	Ferrous sulfate + Folic acid + Cyanocobalamin
	Ferrous sulfate + Folic acid
	Ferrous fumarate + Folic acid

and any other substances affecting hematopoiesis (for example, cytostatic agents, interferons, chloramphenicol, streptomycin).

- Other substances that influence hematopoiesis (epoetins, anabolic steroids, etc.)
- Medicinal products that slow iron absorption (antacids, calcium supplements), 2 hours before administration of the investigational products. It is not recommended to drink strong tea and coffee 2 hours before the administration of medicinal products.

During the study, the patients must not undergo physiotherapy or other procedures that potentially affect erythropoiesis (for example, Buteyko breathing).

8. Efficacy analysis

8.1. Primary endpoint analysis

- Changes in hemoglobin level (g/L) after 12 weeks of iron deficiency therapy (at the final visit) as compared to baseline (determined at the screening visit) in the study groups.

The covariance analysis (ANCOVA) will be used as the main method for assessing the primary endpoint, with the baseline blood hemoglobin level as a covariate, and four fixed factors (treatment group, sex, weight, and baseline hemoglobin level (80–94 g/L vs. 95–110 g/L). The method of unrestricted least significant differences (LSD) will be applied to ANCOVA results with LS mean values from 95% CI for mean values calculated by the method of least squares for differences between the studied groups. Due to the obvious dependence of the covariates and the base hemoglobin factor (80–94 g/L compared to 95–110 g/L), a linear model containing the term of interaction between these variables will be used.

Non-inferiority will be confirmed if the upper bound of a two-sided confidence interval for the mean value calculated by the method of least squares does not exceed the predetermined non-inferiority margin of 5 g/L. The CI percentage will be determined by the moment of the analysis (interim/final) in accordance with clause 2.3 of the Statistical Analysis Plan.

8.2. Analysis of the secondary endpoint

- Absolute values and changes in hemoglobin level (g/L) after 4, 8, and 12 weeks of therapy (determined at the final visit) between the study groups.
- Changes in iron metabolism parameters mean values (ferritin, transferrin, percent transferrin saturation, serum iron) during the therapy period (from the screening to the study end visit) in the study groups.
- The responder rate (%) was determined as an increase in the hemoglobin level by ≥ 20 g/L after 12 weeks of treatment (from screening to the study end visit) in the study groups.

The data will be checked for compliance with the normal distribution law using the Shapiro–Wilk test.

Intergroup comparison of secondary endpoints related to quantitative scales will be performed using Student's t-test for independent samples if the data correspond to the normal distribution law; otherwise, the Mann–Whitney U test will be applied to independent samples.

Intergroup comparisons of secondary endpoints related to categorical scales will be performed using Pearson's chi-square test if the number of points in each cell of the crosstab is ≥ 5, or Fisher's exact test if at least one of the crosstab cells contains < 5 points.

The dynamics will be assessed using ANOVA methods with repeated measurements if the data correspond to the normal distribution; otherwise, the Friedman test will be applied.

9. Safety analysis

Safety evaluation of the study therapy will be performed throughout the study and will be based on the detection of any adverse events occurring during the study. The following will be performed:

- Physical examination, including measurement of blood pressure and heart rate, and gastrointestinal disorders identification (at the screening, during the second visit, and the final visit).
- Complete blood count (at screening and in 4, 8, and 12 weeks of treatment);
- Blood biochemistry (at screening and after 12 weeks of treatment);
- Clinical urinalysis, pregnancy test (at screening and in 12 weeks);
- Registration of concomitant therapy (at each visit).

9.1. Adverse events

The safety assessment will include determining the total number, frequency, and severity of:

1. Adverse events (AEs), regardless of their relation to the treatment;
2. AEs associated or potentially associated with the medicinal product;
3. AEs requiring treatment discontinuation.

Adverse events will be coded using the MedDRA nomenclature in the latest version. These will be represented by the preferred term (PT) and systemic organ class (SOC).

Methods of descriptive statistics will be used to represent the results. Comparison of the incidence of new cases of AE in the study groups will be carried out using Fisher's exact test or Pearson's χ^2 test, depending on the number of observations in one cell (< 5 or ≥ 5).

Changes in the results of laboratory tests over time and the incidence of abnormal test results (based on the reference values of the central laboratory) will be summarized by groups, and a comparison will be made between the groups using appropriate tests for quantitative and qualitative data.

Safety data will be analyzed using the methods designated for the application of efficacy data evaluation.

9.2. Other safety endpoints

No other safety endpoints are foreseen in this study.

10. Exploratory analysis

In the course of this study, exploratory analysis is not envisaged.

11. Interim analysis

One interim analysis is planned to assess the primary and secondary efficacy endpoints when a group of patients with available data on the primary endpoint will include at least 200 subjects [100 patients in each treatment group: in the main treatment group of patients taking Ferrum Lek® (iron (III) hydroxide polymaltosate complex) and in the control group of patients taking MALTOFER® (iron (III) hydroxide polymaltosate complex]. Safety and efficacy will be assessed in all patients who have received at least one dose of randomized therapy at the time of the interim analysis. Based on the results of the interim analysis of the primary and secondary statistical endpoints of efficacy and safety, the Sponsor may decide to discontinue the study if the endpoints of the study are achieved in accordance with the protocol based on the results of the interim analyses or the sample size can be recalculated using the results of the interim analysis.

Appendix 1. Table layouts

PRIMARY ENDPOINT

Parameter	Coef.	Standard error	*t*-value	*p*-value	CI	
Constant (intercept)						
Group R versus Group T						
Gender M versus F						
Weight						
Base hemoglobin factor (80–94 g/L compared to 95–110 g/L)						
Hemoglobin level at screening						
Interactions						

SECONDARY ENDPOINTS

Table 1. Hemoglobin, frequency analysis of the treatment efficacy after 12 weeks

Hemoglobin (g/L)		
Group	Parameter	Value
R – Maltofer®	Total observations	
	Responders, n	
	Responders, %	
	95% CI	
T – Ferrum Lek®	Total observations	
	Responders, n	
	Responders, %	
	95% CI	
Group comparison	Pearson's chi-square test, p-value	

Table 2. Results of analysis of variance

Coefficients	Evaluation	Standard error	t-value	p-value
(Intercept)				
V1_CB_LBORRES_HB *(Hemoglobin level at screening)*				
Group T – Ferrum Lek® *(Test to reference group factor)*				

Table 3. Hemoglobin, absolute values, g/L

Hemoglobin (g/L)					
Group	**Parameter**	**Screening**	**Week 4**	**Week 8**	**Week 12**
R – Maltofer®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				

	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
T – Ferrum Lek®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				
	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
Group comparison	Criterion				
	p-value				

Table 4. Hemoglobin, changes, g/L

Hemoglobin (g/L)				
Group	**Parameter**	**Week 4 – Screening**	**Week 8 – Screening**	**Week 12 – Screening**
R – Maltofer®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			
	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
T – Ferrum Lek®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			
	Minimum value			

	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
Group comparison	Criterion			
	p-value			

Table 5. Blood serum iron, absolute values, µmol/L

Serum iron level (µmol/L)					
Group	**Parameter**	**Screening**	**Week 4**	**Week 8**	**Week 12**
R – Maltofer®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				

	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
T – Ferrum Lek®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				
	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
Group comparison	Criterion				
	p-value				

Table 6. Blood serum iron, changes, µmol/L

Serum iron level (µmol/L)				
Group	**Parameter**	**Week 4 – Screening**	**Week 8 – Screening**	**Week 12 – Screening**
R – Maltofer®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			
	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
T – Ferrum Lek®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			
	Minimum value			

	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
Group comparison	Criterion			
	p-value			

Table 7. Transferrin, absolute values, g/L

Transferrin (g/L)					
Group	**Parameter**	**Screening**	**Week 4**	**Week 8**	**Week 12**
R – Maltofer®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				
	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
T – Ferrum Lek®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				

	Minimum value				
	Maximum value				
	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
Group comparison	Criterion				
	p-value				

Table 8. Transferrin, changes, g/L

Transferrin (g/L)				
Group	**Parameter**	**Week 4 – Screening**	**Week 8 – Screening**	**Week 12 – Screening**
R – Maltofer®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			
	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
T – Ferrum Lek®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			

	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
Group comparison	Criterion			
	p-value			

Table 9. Percentage of transferrin saturation with iron, absolute values (%)

Percentage of transferrin saturation with iron (%)					
Group	**Parameter**	**Screening**	**Week 4**	**Week 8**	**Week 12**
R – Maltofer®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				

	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
T – Ferrum Lek®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				
	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
Group comparison	Criterion				
	p-value				

Table 10. Percentage of transferrin saturation with iron, changes (%)

Percentage of transferrin saturation with iron (%)				
Group	**Parameter**	**Week 4 – Screening**	**Week 8 – Screening**	**Week 12 – Screening**
R – Maltofer®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			
	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
T – Ferrum Lek®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			

	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
Group comparison	Criterion			
	p-value			

Table 11. Ferritin, absolute values, µg/L

Serum ferritin level (µg/L)					
Group	**Parameter**	**Screening**	**Week 4**	**Week 8**	**Week 12**
R – Maltofer®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				
	Standard deviation				
	Median				
	Minimum value				
	Maximum value				
	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
T – Ferrum Lek®	Number of observations				
	Number of missing values				
	Mean value				
	95% CI				

	Standard deviation				
	Median				
	Minimum value				
	Maximum value				
	1st quartile				
	3rd quartile				
	Interquartile range				
	p-value (Shapiro–Wilk test)				
Group comparison	Criterion				
	p-value				

Table 12. Ferritin, changes, µg/L

Serum ferritin level (µg/L)				
Group	**Parameter**	**Week 4 – Screening**	**Week 8 – Screening**	**Week 12 – Screening**
R – Maltofer®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			
	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
T – Ferrum Lek®	Number of observations			
	Number of missing values			
	Mean value			
	95% CI			
	Standard deviation			
	Median			

	Minimum value			
	Maximum value			
	1st quartile			
	3rd quartile			
	Interquartile range			
	p-value (Shapiro–Wilk test)			
Group comparison	Criterion			
	p-value			

LABORATORY RESULTS

Table 1. Urinalysis

Visit	Group	Parameter	pH	Protein	Specific gravity	RBC
V1	Treatment group: R – Maltofer®	N				
		Missed				
		Beyond the limit of detection				
		Mean				
		95% CI				
		SD				
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				
		IQR.75%				
	Treatment group: T – Ferrum Lek®	N				
		Missed				
		Beyond the limit of detection				
		Mean				

Visit	Group	Parameter	pH	Protein	Specific gravity	RBC
		95% CI				
		SD				
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				
		IQR.75%				
V5	Treatment group: R – Maltofer®	N				
		Missed				
		Beyond the limit of detection				
		Mean				
		95% CI				
		SD				
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				
		IQR.75%				
		N				

Visit	Group	Parameter	pH	Protein	Specific gravity	RBC
	Treatment group: T – Ferrum Lek®	Missed				
		Beyond the limit of detection				
		Mean				
		95% CI				
		SD				
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				
		IQR.75%				

Table 2. Urinalysis statistical test

Visit		V1	V5	V1	V5	V1	V5	V1	V5
Variable		pH		Protein		Specific gravity		RBC	
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®								
	Treatment group: T – Ferrum Lek®								
Student's t-test, p-value									
Wilcoxon–Mann–Whitney test, p-value									

Table 3. Urinalysis, categorical variables

Visit	Variable	Group	Distribution of responses	Chi-square test, p-value
V1	WBC	Treatment group: R – Maltofer®		
		Treatment group: T – Ferrum Lek®		
	Color	Treatment group: R – Maltofer®		
		Treatment group: T – Ferrum Lek®		
V5	WBC	Treatment group: R – Maltofer®		
		Treatment group: T – Ferrum Lek®		
	Color	Treatment group: R – Maltofer®		
		Treatment group: T – Ferrum Lek®		

Table 4. Hematology 1

Visit	Group	Parameter	Hematocrit (%)	Hemoglobin	RBC
V1	Treatment group: R – Maltofer®	N			
		Missed			
		Beyond the limit of detection			
		Mean			

Visit	Group	Parameter	Hematocrit (%)	Hemoglobin	RBC
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
	Treatment group: T – Ferrum Lek®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
V3	Treatment group: R – Maltofer®	N			
		Missed			

Visit	Group	Parameter	Hematocrit (%)	Hemoglobin	RBC
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
	Treatment group: T – Ferrum Lek®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			

Visit	Group	Parameter	Hematocrit (%)	Hemoglobin	RBC
		IQR.75%			
V4	Treatment group: R – Maltofer®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
	Treatment group: T – Ferrum Lek®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			

Visit	Group	Parameter	Hematocrit (%)	Hemoglobin	RBC
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
V5	Treatment group: R – Maltofer®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
	Treatment group: T – Ferrum Lek®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			

Visit	Group	Parameter	Hematocrit (%)	Hemoglobin	RBC
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			

Table 5. Hematology 2

Visit	Group	Parameter	WBC	Lymphocytes	Lymphocytes (%)
V1	Treatment group: R – Maltofer®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			

Visit	Group	Parameter	WBC	Lymphocytes	Lymphocytes (%)
	Treatment group: T – Ferrum Lek®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			

Table 6. Hematology 3

Visit	Group	Parameter	Neutrophils	Neutrophils (%)	Stab neutrophils (%)	Segmented neutrophils (%)
V1	Treatment group: R – Maltofer®	N				
		Missed				
		Beyond the limit of detection				
		Mean				
		95% CI				
		SD				

Visit	Group	Parameter	Neutrophils	Neutrophils (%)	Stab neutrophils (%)	Segmented neutrophils (%)
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				
		IQR.75%				
	Treatment group: T – Ferrum Lek®	N				
		Missed				
		Beyond the limit of detection				
		Mean				
		95% CI				
		SD				
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				
		IQR.75%				

Table 7. Hematology 4

Visit	Group	Parameter	Basophils	Basophils (%)	ESR	Platelets	Eosinophils	Eosinophils (%)
V1	Treatment group: R – Maltofer®	N						
		Missed						
		Beyond the limit of detection						
		Mean						
		95% CI						
		SD						
		Median						
		Min						
		Max						
		Q1.25%						
		Q3.75%						
		IQR.75%						
	Treatment group: T – Ferrum Lek®	N						
		Missed						
		Beyond the limit of detection						
		Mean						
		95% CI						
		SD						

Visit	Group	Parameter	Basophils	Basophils (%)	ESR	Platelets	Eosinophils	Eosinophils (%)
		Median						
		Min						
		Max						
		Q1.25%						
		Q3.75%						
		IQR.75%						

Table 8. Hematology, statistical test 1

Visit		V1	V3	V4	V5	V1	V3	V4	V5	V1	V3	V4	V5
Variable		Hematocrit (%)				Hemoglobin				RBC			
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®												
	Treatment group: T – Ferrum Lek®												
Student's t-test, p-value													
Wilcoxon–Mann–Whitney test, p-value													

Table 9. Hematology, statistical test 2

Visit		V1		
Variable		WBC	Lymphocytes	Lymphocytes (%)
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®			
	Treatment group: T – Ferrum Lek®			
Student's t-test, p-value				
Wilcoxon–Mann–Whitney test, p-value				

Table 10. Hematology, statistical test 3

Visit	V1

Variable		Neutrophils	Neutrophils (%)	Stab neutrophils (%)	Segmented neutrophils (%)
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®				
	Treatment group: T – Ferrum Lek®				
Student's t-test, p-value					
Wilcoxon–Mann–Whitney test, p-value					

Table 11. Hematology, statistical test 4

Visit		V1					
Variable		Basophils	Basophils (%)	ESR	Platelets	Eosinophils	Eosinophils (%)
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®						
	Treatment group: T – Ferrum Lek®						
Student's t-test, p-value							
Wilcoxon–Mann–Whitney test, p-value							

Table 12. Physiological data

Visit	Group	Parameter	Weight	Age	BMI	Height
V1	Treatment group: R – Maltofer®	N				
		Missed				

Visit	Group	Parameter	Weight	Age	BMI	Height
		Beyond the limit of detection				
		Mean				
		95% CI				
		SD				
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				
		IQR.75%				
	Treatment group: T – Ferrum Lek®	N				
		Missed				
		Beyond the limit of detection				
		Mean				
		95% CI				
		SD				
		Median				
		Min				
		Max				
		Q1.25%				
		Q3.75%				

Visit	Group	Parameter	Weight	Age	BMI	Height
		IQR.75%				

Table 13. Physiological data, statistical test

Visit		V1			
Variable		Weight	Age	BMI	Height
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®				
	Treatment group: T – Ferrum Lek®				
Student's t-test, p-value					
Wilcoxon–Mann–Whitney test, p-value					

Table 14. Physiological data, categorical data

Visit	Variable	Group	Distribution of responses	Chi-square test, p-value
V1	Gender	Treatment group: R – Maltofer®		
		Treatment group: T – Ferrum Lek®		

Table 15. Biochemistry 1

Visit	Group	Parameter	ALT	AST	Total protein	Total bilirubin	C-reactive protein
V1	Treatment group: R – Maltofer®	N					
		Missed					

Visit	Group	Parameter	ALT	AST	Total protein	Total bilirubin	C-reactive protein
		Beyond the limit of detection					
		Mean					
		95% CI					
		SD					
		Median					
		Min					
		Max					
		Q1.25%					
		Q3.75%					
		IQR.75%					
	Treatment group: T – Ferrum Lek®	N					
		Missed					
		Beyond the limit of detection					
		Mean					
		95% CI					
		SD					
		Median					
		Min					
		Max					
		Q1.25%					

Visit	Group	Parameter	ALT	AST	Total protein	Total bilirubin	C-reactive protein
		Q3.75%					
		IQR.75%					
V5	Treatment group: R – Maltofer®	N					
		Missed					
		Beyond the limit of detection					
		Mean					
		95% CI					
		SD					
		Median					
		Min					
		Max					
		Q1.25%					
		Q3.75%					
		IQR.75%					
	Treatment group: T – Ferrum Lek®	N					
		Missed					
		Beyond the limit of detection					
		Mean					
		95% CI					
		SD					

Visit	Group	Parameter	ALT	AST	Total protein	Total bilirubin	C-reactive protein
		Median					
		Min					
		Max					
		Q1.25%					
		Q3.75%					
		IQR.75%					

Table 16. Biochemistry 2

Visit	Group	Parameter	Conjugated bilirubin	Creatinine level	Alkaline phosphatase
V1	Treatment group: R – Maltofer®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			

Visit	Group	Parameter	Conjugated bilirubin	Creatinine level	Alkaline phosphatase
	Treatment group: T – Ferrum Lek®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
V5	Treatment group: R – Maltofer®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			

Visit	Group	Parameter	Conjugated bilirubin	Creatinine level	Alkaline phosphatase
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			
	Treatment group: T – Ferrum Lek®	N			
		Missed			
		Beyond the limit of detection			
		Mean			
		95% CI			
		SD			
		Median			
		Min			
		Max			
		Q1.25%			
		Q3.75%			
		IQR.75%			

Table 17. Biochemistry 3

Visit	Group	Parameter	T4	Vitamin B12	Creatinine index	TSH	Folic acid (B9)
V1	Treatment group: R – Maltofer®	N					
		Missed					

Visit	Group	Parameter	T4	Vitamin B12	Creatinine index	TSH	Folic acid (B9)
		Beyond the limit of detection					
		Mean					
		95% CI					
		SD					
		Median					
		Min					
		Max					
		Q1.25%					
		Q3.75%					
		IQR.75%					
	Treatment group: T – Ferrum Lek®	N					
		Missed					
		Beyond the limit of detection					
		Mean					
		95% CI					
		SD					
		Median					
		Min					
		Max					
		Q1.25%					

Visit	Group	Parameter	T4	Vitamin B12	Creatinine index	TSH	Folic acid (B9)
		Q3.75%					
		IQR.75%					

Table 18. Biochemistry, statistical test 1

Visit		V1	V5	V1	V5	V1	V5	V1	V5	V1	V5
Variable		ALT		AST		Total protein		Total bilirubin		C-reactive protein	
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®										
	Treatment group: T – Ferrum Lek®										
Student's t-test, p-value											
Wilcoxon–Mann–Whitney test, p-value											

Table 19. Biochemistry, statistical test 2

Visit		V1	V5	V1	V5	V1	V5
Variable		Conjugated bilirubin		Creatinine level		Alkaline phosphatase	
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®						
	Treatment group: T – Ferrum Lek®						
Student's t-test, p-value							
Wilcoxon–Mann–Whitney test, p-value							

Table 20. Biochemistry, statistical test 3

Visit		V1				
Variable		T4	Vitamin B12	Creatinine index	TSH	Folic acid (B9)
Shapiro–Wilk test, p-value	Treatment group: R – Maltofer®					
	Treatment group: T – Ferrum Lek®					
Student's t-test, p-value						
Wilcoxon–Mann–Whitney test, p-value						

ADVERSE EVENTS

Table 1. Adverse events reported in the study

Adverse events	Group	Amount	% of the total number of AEs	% of the number of AEs by the medicinal product	p-value, Fisher's test
All adverse events	T				
	R				
SOC...	T				
	R				
PT...	T				
	R				
PT...	T				
	R				
	T				
	R				
SOC...	T				
	R				
PT...	T				
	R				
PT...	T				
	R				
	T				
	R				

Tables N. Is the adverse event ongoing?/ Relatedness to the medicinal product/ Dose adjustment or temporary withdrawal of the IMP/ Complete withdrawal of the IMP/ Prescribing a concomitant medicinal product/ Prescribing non-drug therapy/ Patient admission to hospital or hospitalization prolongation/ Based on an AE/ Is it an SAE?/ Leads to death/ Threatens life/ Requires admission to hospital or hospitalization prolongation/ Leads to permanent or significant incapacity for work or disability

Adverse events	Group	{variable name]	Amount	% of the number of AEs by the medicinal product	p-value, Fisher's test
All adverse events	T	value			1
		value			
		value			
	R	value			
		value			
		value			
SOC...	T	value			1
		value			
		value			
	R	value			
		value			
		value			
PT...	T	value			1
		value			
		value			
	R	value			
		value			
		value			

Adverse events	Group	{variable name]	Amount	% of the number of AEs by the medicinal product	p-value, Fisher's test
PT...	T	value			1
		value			
		value			
	R	value			
		value			
		value			
	T	value			1
		value			
		value			
	R	value			
		value			
		value			
SOC...	T	value			1
		value			
		value			
	R	value			
		value			
		value			
PT...	T	value			1
		value			
		value			
	R	value			

Adverse events	Group	{variable name]	Amount	% of the number of AEs by the medicinal product	p-value, Fisher's test
		value			
		value			
PT...	T	value			1
		value			
		value			
	R	value			
		value			
		value			
	T	value			1
		value			
		value			
	R	value			
		value			
		value			