Cover Page

Pilot Study to Gain First Indications for the Impact of a Three-month's Oral Intake of an Iron Supplement ith High Bioavailability on the Hemoglobin Concentration in Iron Deficient Blood Donors

NTC04250298

Study Protocol and Statistical Analysis Plan

Version 1 of 2019/05/15 (original)

Version 1.1 (translated into English on 2023/02/19)

Pilot study to obtain first evidence on the influence of a three-month oral intake of an iron supplement with high bioavailability (OLEOvital® EISEN FORTE) on hemoglobin concentration in whole blood donors with iron deficiency.

Short description:

Study of sucrosomal iron supplementation in blood donors.

Dr. Camilla Drexler (Principal investigator)

Dr. Petra Krakowitzky (Deputy Study Director)

Dr. Patrick Paul Torreiter (study collaborator)

University Department of Blood Group Serology and Transfusion Medicine

LKH - University Hospital Graz

Auenbruggerplatz 48

A-8036 Graz

Study Center:

University Department of Blood Group Serology and Transfusion Medicine

LKH - University Hospital Graz

Auenbruggerplatz 48

A-8036 Graz

Head of the clinic: Univ.Prof.Dr. Peter Schlenke

Biometry:

Dr. Wolfgang Schimetta

Working Group for System Optimization of Clinical Research Projects ASOKLIF

Department of Applied Systems Research and Statistics

Johannes Kepler University

Altenbergerstrasse 69

A-4040 Linz

Design:

Monocentric interventional study with 1 cohort.

Study period: 2019 - 2020

INTRODUCTION/BACKGROUND:

Iron deficiency or iron deficiency anemia is a common phenomenon among regular blood donors and is observed in up to 50% of male and up to 75% of female donors.1 Predisposing factors are female sex, low weight, and high blood donation frequency.2-4 A whole blood donation results in blood loss of 200-300 mg of iron.5-7 The average daily iron absorption is 1-2 mg iron and can only be moderately increased.8 Kiss et al demonstrated that blood donors with iron deficiency are often unable to reach 80% of baseline hemoglobin without iron supplementation within 180 days after whole blood donation,9 therefore iron therapy for iron deficiency seems reasonable for prophylaxis of anemia in blood donors.

Conventional oral iron therapy with iron sulfates, citrates, or fumarates is well established and has been in use for decades. However, higher iron doses are not possible with this because upregulation of hepcidin results in inhibition of iron absorption.10,11 For this reason, iron in this form must be administered in low doses or alternately with a one-day break. This is impractical and lengthy, especially for otherwise healthy individuals such as blood donors, who often take no other medications at all. In addition, dosing regimens must be followed, and therapy is often associated with gastrointestinal side effects. This can lead to discontinuation of therapy without replacement and also to no checks of the iron balance at the family doctor.

New dietary supplements such as oral sucrosomal iron (OLEOvital® EISEN FORTE) are promising due to their high bioavailability, good tolerability and ease of use and have been successfully tested, for example, in patients with chronic renal insufficiency12 or in pregnant women without anemia13. Based on these positive properties, it is expected that there is a high suitability for otherwise healthy blood donors. Our aim is to collect initial data on the efficacy of the preparation in whole blood donors with iatrogenic iron deficiency in a pilot study, evaluating the setting and feasibility of a randomized controlled follow-up study with a sufficiently large donor population.

The donor population planned for the study corresponds to a group with iron deficiency (ferritin <30 ng/ml), in which case a steady state of iron balance cannot be guaranteed.9 A spontaneous increase in Hb levels, which would also occur without iron supplementation, could thus influence the study results. This circumstance will be taken into account in the interpretation of the results and included in the evaluation.

The donor population planned for the study corresponds to a group with iron deficiency (ferritin <30 ng/ml), in which case a steady state of iron balance cannot be guaranteed.9 A spontaneous increase in Hb levels, which would also occur without iron supplementation, could thus influence the study results. This circumstance will be taken into account in the interpretation of the results and included in the evaluation.

STUDY OBJECTIVE:

The objective of this pilot study, which follows a descriptive/exploratory approach, is to investigate the effects of three months of OLEOvital® IRON FORTE supplementation in whole blood donors with iron deficiency. In detail it is about

- to gain initial insights into the extent of the change in primary hemoglobin and secondary ferritin concentrations,

- the observation of the acceptance and tolerability of a test product intake of several months,

- the generation of pilot data for a subsequently planned randomized controlled trial.

In the case of changes in hemoglobin and ferritin concentrations, a primary objective of the study is not only to look at the total collective but also to preliminarily compare the two sub-collectives (pre-menopausal women vs. post-menopausal women or men.

STUDY DESIGN:

The present monocentric study (single cohort design) is to be classified as a food study (use of the commercially available food supplement OLEOvital® EISEN FORTE) in an interventional setting (study-specific measures: additional blood testing and intake of OLEOvital® EISEN FORTE).

A total of 50 whole blood donors defined as inclusions accepted for intent-to-treat analysis will be included in the study. This will include 25 pre-menopausal women (in subcollective 1) and 25 post-menopausal women or men (in subcollective 2). Subcollective 2 will include at least 10 men and at least 10 women.

SELECTION OF STUDY PARTICIPANTS:

Inclusion criteria:

- Exclusion from blood donation if capillary hemoglobin (Hb) <12.5g/dl (♀) or Hb <13.5g/dl (♂) is too low.

- Otherwise, eligibility for blood donation according to medical history form.

- Ferritin at the time of exclusion from donation <30ng/mL.

- Last whole blood donation >2 months prior to current hemoglobin value.

- Written informed consent after previous written and verbal informed consent.

- Venous hemoglobin (Hb) <12.5g/dl (♀) or Hb <13.5g/dl (♂).

Exclusion criteria:

- Incapacitated or court-ordered adult representation.

- Known pregnancy

- Breastfeeding period

- Chronic diarrhea or known diarrhea tendency

- Known or suspected fructose intolerance

- Taking an iron supplement in the past three months

- Permanent or expected blood loss (e.g., oozing bleeding)

- Hypermenorrhea

- Planned surgical procedure with relevant blood loss within the next 3-4 months (during the duration of the study)

- Application of another iron-supplementing preparation within the next 3-4 months

- Intended use of preparations for the targeted increase of endogenous red cell or hemoglobin concentration or production (e.g. EPO preparations, Ery concentrates) for the duration of the study

- Simultaneous participation in another clinical trial with insurance coverage

- Foreseeable compliance problems

- Foreseeable unavailability for the final examination

- Intolerance to any of the components of the investigational product

- Acute anemia requiring therapy: Hb < 8 g/dl (indication for mandatory correction of Hb to a clinically irrelevant or non-therapy requiring value)

TEST PRODUCT:

OLEOvital® IRON FORTE:

- Manufacture:

Pharmanutra S.p.a., Pisa, Italy.

- Distribution:

Fresenius Kabi Austria GmbH, A-8055 Graz, Austria.

- Status:

Food supplement

- Composition:

1 sachet or 1 capsule contains:

30mg iron and 70mg vitamin C

Sucrosomal® formulation of iron:

Ferric pyrophosphate, rice starch; emulsifier: sugar esters of fatty acids, lecithins, glucose syrup, milk protein, tricalcium phosphate.

Other ingredients of the powder (applies only to sachets):

Xylitol, sorbitol, acesulfame K, sucralose.

Gluten and lactose free

For further details, see product information in the project plan appendix

Intake:

- 1 sachet or capsule per day (i.e., 30 mg of iron per day; total of 90 to a maximum of 120 sachets or capsules, i.e., 2,700 to a maximum of 3,600 mg of iron within 90 to a maximum of 120 days)

- Oral intake at any time of the day; no consideration of simultaneous intake of medications, food or beverages

- The contents of a sachet are dissolved directly in the mouth and swallowed without water; the capsules are taken with sufficient liquid.

BASIC/ADJUNCTIVE MEDICATION AND CONCOMITANT MEASURES:

Adverse Medication and Concomitant Measures:

During the entire study participation (except for the investigational product), if possible, no use/ingestion of drugs, dietary supplements, or dietary foods for iron supplementation or to specifically increase endogenous red blood cell or hemoglobin concentration or production (e.g., EPO preparations, Ery concentrates) - use/ingestion of such products will result in classification of the case in question as a drop out.

Otherwise no restrictions

EXAMINATIONS:

- U1 = (entry) examination (donor inclusion) on day 0.

- U2 = (final) examination (study participation completion) at Day 90 (tolerance margin + 30 days).

Investigations:

	U1	U2
Date [DDMMYYY]	✓	✓
Date of blood collection [DDMMYYY]	✓	
Gender [m/f]*	✓	

Age [years]*	✓	
Body height [cm]*	✓	
Body weight [kg]*	✓	
Relevant previous medication [narrative]	✓	
Relevant previous diseases [narrative]	✓	
Hb [g/dl]	✓	✓
Serum ferritin [ng/ml]	✓	✓
Version of OLEOvital® EISEN FORTE [sachets / capsules]	✓	
Evaluation of taking OLEOvital® EISEN FORTE [without problems yes/no]*		✓
Problems with taking OLEOvital® EISEN FORTE [narrative]*		✓
Recommendation of taking OLEOvital® EISEN FORTE for other blood donors [yes/no]*		✓
Taking OLEOvital® EISEN FORTE again in the given case [yes/no]*		✓
Test product intake [number of sachets or capsules taken, number of days with violation of intake instructions]		✓
Diarrhea [days]		✓
Applicability of a drop-out criterion [narrative]		✓
Relevant medication [narrative]	← ✓ →	
Relevant concomitant measures [narrative]	← ✓ →	
Concomitant conditions [narrative]	← ✓ →	
Serious Adverse Events [form: narrative]	← ✓ →	
Suspected investigational product adverse events [form: narrative]	← ✓ →	
Baseline information questionnaire on possible clinical symptoms of iron deficiency and evaluation of OLEOvital® EISEN FORTE [narrative, categories]	✓	✓
Health-related quality of life questionnaire (WHOQOL-Bref)	✓	✓
Fatigue questionnaire (FAQ) [-]	✓	✓
Mental Symptoms of Insomnia Questionnaire (RIS) [-]	✓	✓
Restless Legs Syndrome (RLS) [yes/no]	✓	✓
In pre-menopausal women: time since end of last menstrual period before blood draw [days]*	✓	✓
In pre-menopausal women: menstrual periods between blood draws [number]*		✓

* Inclusion in the questionnaire of basic information on possible clinical symptoms of an iron deficiency and for the evaluation of OLEOvital® EISEN FORTE

STUDY PARAMETERS:

Target parameter:

- Hb to U2 [g/dl]
- Delta Hb U1-U2 [g/dl]
- Delta Hb U1-U2 / 90 days [g/dl]
- Delta Hb U1-U2 * Ratio of prescribed/taken sachets or capsules / 90 days [g/dl]
- Response I (delta Hb U1-U2 /90 days ≥1.0g/dl) [yes/no]
- Response II (Delta Hb U1-U2 /90 days ≥1.5g/dl) [yes/no]
- Response III (delta Hb U1-U2 /90 days ≥2.0g/dl) [yes/no]
- Ferritin to U2 [µg/l]
- Delta ferritin U1-U2 [ng/ml]
- Delta ferritin U1-U2 / 90 days [ng/ml]
- Delta ferritin U1-U2 * ratio prescribed/taken sachets or capsules / 90 days [ng/ml]
- Evaluation of the intake of OLEOvital® EISEN FORTE [without problems yes/no].
- Problems with taking OLEOvital® EISEN FORTE [categories by type]
- Recommendation of taking OLEOvital® EISEN FORTE for other blood donors [yes/no]
- Re-administration of OLEOvital® EISEN FORTE in the given case [yes/no].
- Suspected test product side effects [categories by type and severity, duration].
- Items of the questionnaire on baseline information on possible clinical symptoms of iron deficiency and evaluation of OLEOvital® EISEN FORTE (Part B at U2) [narrative, categories]
- WHOQOL-Bref (domain scores) at U2 [-]
- Delta WHOQOL-Bref (domain scores) U1-U2 [-]
- FAQ at U2 [-]
- Delta FAQ U1-U2 [-]
- RIS at U2 [-]
- Delta RIS U1-U2 [-]
- RLS [yes/no] at U2

Other parameters:

- Hb at U1 [g/dl]
- Ferritin at U1 [µg/l]
- Items of the questionnaire on basic information on possible clinical symptoms of iron deficiency and on the evaluation of OLEOvital® EISEN FORTE (part A at U1) [narrative, categories].
- WHOQOL-Bref (domain scores) on U1 [-]
- FAQ at U1 [-]
- RIS at U1 [-]
- RLS [yes/no] at U1
- Age at U1 [years]
- Gender [♀/♂]
- Body weight at U1 [kg]
- Body height at U1 [cm]
- BMI at U1 [kg/m²]
- Intake of OLEOvital® EISEN FORTE [sachets / capsules].

- Intake of sachets or capsules [number of sachets or capsules taken and ratio taken/prescribed, number of days with violation of intake instructions]
- Diarrhea [days]
- Drop-out criteria [categories based on chapter of the same name].
- Relevant (already discontinued) prior medication [categories by type].
- Relevant medication at U1 as well as U1-U2 [categories by type and duration of use].
- Relevant (already cured) previous diseases [categories by type]
- Concomitant diseases at U1 as well as U1-U2 [categories by type, change/new occurrence/absence, duration of disease]
- Serious adverse events [categories by type and duration]
- Time intervals U1-U2, 1st blood draw - U1 and 1st blood draw - U2 [days].
- Time interval end of last menstrual period to blood draw for U1 [days].
- Time interval end of last menstrual period until U2 [days]
- Menstrual bleeding between blood draws [number]

METHODS:

Study participant recruitment and study participation:

A donor determined to be eligible in principle for the study during routine Hb and ferritin screening will be contacted by telephone and invited to participate in the study. During the telephone call, the general eligibility criteria are queried. If the donor agrees, he/she will receive an appointment at the study center, which must take place no later than 3 weeks after the date of the last blood draw. The donor will be informed that no iron tablets may be taken in the meantime and that he/she is not allowed to donate blood.

If the donor attends the appointment at the study center, a detailed written and verbal explanation will be given and the donor's written consent to participate in the study will be requested. If this consent is given and it is then definitively established that all inclusion criteria are met and that all exclusion criteria are not met, the donor is enrolled in the study.

Study participation begins with the (initial) U1 examination, during which relevant previous medication and relevant previous illnesses are recorded. Furthermore, the study participant is asked to fill out 4 questionnaires.

Finally, the study participant will be given the test products (4 packs of 30 sachets or capsules each - depending on the study participant's preference) and their intake will be explained (instructions for use will be provided - see project plan appendix). In addition, an appointment is made for the final examination U2 (90 days after U1 with a tolerance margin of + 30 days). The study participant is asked to bring all 4 packs (empty or used or not yet used - all unused sachets or capsules should be included) to the (final) examination and to return them.

The donor must be subjectively healthy for the final examination. If this is not the case due to a minor illness (e.g. respiratory infection), the final examination will be postponed. If the tolerance margin for the postponement is not sufficient, the final examination will still be performed at the earliest possible time.

The (final) examination U2 is performed at the same time of day as U1 (i.e., usually in the morning) and includes the study-specific collection of 6 ml of EDTA and 9 ml of native blood for the purpose of determining the intended laboratory parameters. Furthermore, adverse events (with or without reference to the study product), concomitant diseases, relevant concomitant measures, relevant medication and any drop-out criteria are researched and queried. The study participant will also be asked again to complete 4 questionnaires.

The residual amount of study product brought along will be counted, confiscated and destroyed. Thereafter, the donor's study participation is terminated.

Each donor can only participate in the study once.

Laboratory tests:

Venous hemoglobin

Photometric measurement using the cyanmethemoglobin method from EDTA blood (Advia® 2120/120, Siemens Healthcare Diagnostics, Siemens AG Vienna, Austria) according to test specifications

Ferritin

Measurement from serum using Chemo Luminiscence Immuno Assay on Liaison XL (Diasorin S.p.A., Saluggia, Italy) according to manufacturer's instructions

Questionnaire for basic information on possible clinical symptoms of iron deficiency and evaluation of OLEOvital® IRON FORTE

The questionnaire is a PRO instrument with stand-alone items (no linkage to one or more scores). Iron deficiency, even in the absence of anemia, can be associated with clinical symptoms such as restless legs syndrome,14 fatigue15 or cognitive and physical performance decline.16,17 Other symptoms that have been described in the context of iron deficiency include hair loss,18 brittle nails19 or pica.20 Evaluated questionnaires/scores are used to answer complex questions (see below).

WHOQOL-Bref 21,22

The WHOQOL-Bref is an abbreviated version of the WHOQOL-100 and is used to measure

health-related quality of life (Patient-Reported Outcome or PRO instrument) and contains 26 items. It consists of 4 domain scores (Physical Health, Psychological Health, Social Relationships, Environment) that are administered quasimetrically.

For further details see project plan appendix

Fatigue Assessment Questionnaire (FAQ)23,24.

The FAQ is a fatigue assessment instrument (PRO instrument) and contains 23 items. A total score (sum score with quasimetric handling) is calculated via 3 sub-scores (physical, affective, and cognitive category) and 1 single item.

For further details see project plan appendix

Regensburg Insomnia Scale (RIS)25.

The RIS is used to assess symptoms of psychophysiological insomnia (PRO instrument) and contains 10 items. 3 domains are added to a total score, this is handled quasi-metrically as a sum score.

For further details see project plan appendix

Restless Legs Diagnostic according to Allen 200326

This instrument is used to detect a Restless Legs Syndrome. The items for establishing the diagnosis are integrated into the questionnaire on basic information on possible clinical symptoms of iron deficiency and on the evaluation of OLEOvital® EISEN FORTE.

Known side effects of OLEOvital® EISEN FORTE:

No side effects are listed in the manufacturer's product brochure.

(Serious) adverse events and suspected adverse reactions:

Adverse events are any adverse changes that occurred during a donor's participation in the study, whether or not a relationship to the intervention (taking OLEOvital® EISEN FORTE) is suspected.

The term "adverse events" includes:

- all disturbances of well-being
- all subjective or objective symptoms of disease
- all concomitant diseases and accidents occurring during the study, and
- all clinically relevant (pathological) laboratory changes.

Serious Adverse Events:

A serious adverse event is any adverse event,

that indicates a clear hazard or suggests a precautionary measure.

Considering human clinical experience, this includes the following:

- Fatal and life-threatening events

- Events that result in permanent injury, i.e., that result in permanent impairment or inability to continue living in a previous manner

- Events that result in hospitalization or prolongation of hospital stay

- Possible induction of congenital changes or neoplasia.

Suspected adverse reactions (to OLEOvital® IRON FORTE) are all adverse events for which a relationship with the use of this dietary supplement is classified as certain, probable, or possible (adverse events with classifications of relationship with the use of OLEOvital® IRON FORTE as unlikely are not considered suspected adverse reactions to it).

DROP-OUT CRITERIA:

The following events/situations will result in the affected case being classified as a Drop Out and therefore not considered for Per-Protocol analysis:

- Serious project plan violations
  - Inadmissible or incorrect test product intake: intake of less than 75% of the prescribed sachet or capsule number
  - Improper or incorrect test product ingestion: ingestion violations on more than 25% of the days
  - Use/ingestion of medicinal products, food supplements or dietary foods for iron supplementation or for the targeted increase of the body's own red blood cell or hemoglobin concentration or production (e.g. EPO preparations, Ery concentrates), except for trivial amounts
  - False inclusion
  - Omission of the examination U2
  - Non-compliance with the tolerance margin for the examination U2
- Blood loss (e.g., due to trauma, blood donation, ulcer bleeding, etc.) of more than 200ml within the month prior to Exam U2 or of at least 400ml throughout study participation
- Diarrhea on a total of more than 25% of the days
- Knowledge of pregnancy with associated absence of menstrual bleeding
- Withdrawal of consent for study participation by the donor

TERMINATION OF STUDY PARTICIPATION:

The following events/situations will result in immediate termination of study participation by the respective donor:

- (scheduled) at the time of the U2 study.
- Expiration of the tolerance period for the U2 examination; postponement of the final examination for health reasons is considered an exception to this rule
- Withdrawal of consent to study participation by the donor.
- Detection of a false inclusion prior to initiation of study product intake
- Exitus
- Loss of responsibility for the donor (e.g. also due to an unscheduled hospitalization of the donor)
- Failure of the donor to begin test product ingestion (discontinuation prior to ingestion of the first sachet or capsule)

TREATMENT DISCONTINUATION:

Premature discontinuation of study participation will also result in concurrent discontinuation of study-specific investigational product ingestion.

Furthermore, each study participant is free to discontinue study product intake due to suspected inconvenience (adverse events, suspected side effects, inadequate convenience of ingestion, unpleasant taste, etc.) or for other reasons.

BIOMETRIC EXPERIMENTAL DESIGN AND EVALUATION:

Case-Number Justification:

The selected case number of n = 50 (n = 25 in each of the two subcollectives-premenopausal women and postmenopausal women plus men, respectively), with a postulated drop-out rate of approximately 20% (⍰ approx. 40 valid cases in the overall collective and 20 valid cases in each of the two subcollectives), it should be possible to provide initial findings on whether three months of OLEOvital® EISEN-FORTE supplementation can lead to relevant changes in hemoglobin and ferritin concentrations in whole blood donors with iron deficiency (in the overall collective and in the two subcollectives) and whether there are massive problems with acceptance and tolerability of the test product when taken for several months.

Collectives for Evaluation:

Evaluations of the following collectives will be performed.

- Overall Collective. All inclusions (n=50)

- Subcollective 1: Premenopausal women (n=25).

- Subcollective 2: post-menopausal women plus men (n=25).

All 3 collectives will be analyzed as follows:

Per-protocol analysis:

Inclusion of all inclusions without applying a drop-out criterion (all Valid Cases). All collected parameters will be analyzed. The per-protocol analysis has priority for the efficacy assessment.

Intent-To-Treat Analysis:

Inclusion of all inclusions (Valid Cases + Drop Outs) where test product ingestion at least started (ingestion of at least the first test product sachet or test product capsule). All collected parameters will be analyzed. For safety and practicability considerations, the intent-to-treat analysis is primary.

In addition, all collected parameters are analyzed descriptively in a full-analysis approach of those cases that are not included in the intent-to-treat analysis of the overall collective.

Implausible Values and Missing Values:

Implausible Values:

An Hb or ferritin value is considered implausible if it is obtained

- after an intake/application (beyond the test product intake) of drugs, food supplements or dietary foods for iron supplementation or for the targeted increase of the endogenous erythrocyte or hemoglobin concentration or production (e.g. EPO preparations, Ery concentrates).

- after blood loss (e.g. due to trauma, blood donation, ulcer hemorrhage, etc.) of more than 200ml within the last month before the U2 examination or of at least 400ml during the entire study participation.

Further implausibility classifications may be made by the study management.

Missing Values:

Missing values will not be replaced.

Statistical analysis:

Comparison of subcollective 1 vs. subcollective 2:

Common parametric and nonparametric univariate procedures for comparing independent samples are used (two-sample t-test, Mann-Whitney U test, Fisher's exact test, chi-square homogeneity test; test for normal distribution using Kolmogorov-Smirnov test with Lilliefors significances, $\alpha = 10\%$).

Estimation of true effect size:

Two-sided 95% confidence intervals (depending on the nature of the data sets: parametric, nonparametric, or Clopper-Pearson) are calculated for all parameters.

Multiple regression analyses (per-protocol only):

Dependent variables:

- Delta Hb U1-U2 / 90 days [g/dl].
- Delta ferritin U1-U2 / 90 days [µg/l].

Independent variables:

- (Depending on dependent variable) Hb or ferritin at U1
- Demographic data at U1
- Ratio taken/prescribed sachets or capsules
- diarrhea
- Subcollective
- Relevant (already discontinued) prior medication
- Relevant medication at U1 and U1-U2
- Relevant (already cured) previous diseases
- Concomitant diseases at U1 and U1-U2

Post hoc analyses:

If, after completion of the planned analyses, constellations arise that make one or more post hoc analyses (further subcollective comparisons - e.g., between men and women in subcollective 2 - or regression analyses, etc.) seem useful, such analyses are possible.

Alpha error level:

There is no adjustment of the alpha error level for multiple testing, thus all statistical statements are purely descriptive.

Results presentation:

All documented data are tabulated indicating the number of observed and missing values.

- Nominal scaled data are presented in tables with absolute and relative frequencies.
- Ranked data are presented in tables with absolute and relative frequencies and/or using median, quartiles, minimum and maximum.
- For quantitatively measured data, a representation of the following characteristic values of their distribution is given:
- Minimum
- median
- quartiles
- maximum
- Mean value
- Standard deviation

Graphs (box plots and bar charts) can be created if needed.

Intermediate evaluation:

Intermediate evaluation is not provided a priori.

QUALITY ASSURANCE:

Data are recorded in Case Report Forms (CRFs) and subsequently transferred to a study-specific data file. Plausibility and completeness checks are performed as part of data management.

FORMAL STATUS AND LEGAL ASPECTS:

The study is conducted in accordance with the Declaration of Helsinki (as revised by Fortaleza 2013). The data protection regulations valid in Austria are complied with.

From a formal point of view, the study in question is an academic interventional study, which involves a study-specific risk (see also chapter "Risk/benefit assessment").

Only donors who have documented their written informed consent to participate in the study will be included in the study.

The study will only be started after a positive vote of the responsible ethics committee.

The data of the study participants will be processed and evaluated exclusively in pseudonymized form. (Keeping and storage of a study participant identification list).

All serious adverse events are reported to the responsible ethics committee.

Prior to the start of the documentation phase (before the first donor is included in the study), the study is reported in a publicly accessible registry (study registration).

BENEFIT/RISK ASSESSMENT:

Except for

- the intake / use of the test product (OLEOvital® EISEN FORTE)
- the twice visit to the UBT for U1 and U2,
- the filling in of 4 questionnaires twice
- and the one-time collection of 15 ml of blood,

there are no deviations from routine clinical treatment and diagnostics.

No side effects are known for the test product.

Very rarely, reversible complications such as hematoma or circulatory collapse may occur during blood sampling; extremely rarely, injury to a cutaneous nerve may occur, possibly even with a chronic course. Overall, however, the risk in this regard is extremely low."

For the participating whole blood donors, a possible benefit is that if there is a sufficient response to the test product (working hypothesis of the study), there may be an improvement or even normalization of the Hb values and the iron storage values (symptomatic anemia treatment).

Thus, the benefit-risk assessment for the individual study participant can be clearly positive, neutral or slightly negative. If the knowledge gained is taken into account for further treatment considerations in the case of anemia, it should be possible, after evaluating all aspects, to derive an endorsement of the present study from an ethical point of view.

PUBLICATION OF RESULTS:

The study plan (study design) and the results of the study will be published in a scientific journal under the responsibility of the study director and with the involvement of all other participants in the project implementation (in the case of all signatories of the project plan as co-authors, in the case of all other project participants either as co-authors or in an addendum).

PROJECT PLAN CHANGES:

All project plan amendments shall only become valid if all signatories of the project plan give their consent. The changes are then to be documented by means of addenda or amendments (to be signed in the same way as the project plan) (transmission to all project plan owners).

The study is partially supported by an Unrestricted Grant from Fresenius Kabi Austria GmbH, Graz. Fresenius Kabi Austria GmbH will also provide all required test products free of charge.

For the project plan, a template of the Working Group for System Optimization of Clinical Research Projects (ASOKLIF) was used with their kind permission.

SIGNATURES:

We have read this project plan for the study with the short name "Study of Sucrosomal Iron Supplementation of Blood Donors" dated 01.10.2019 and confirm that it contains all information necessary for the implementation of this project. We intend to conduct the study in accordance with this study plan.

Note:

Signatures of the principal investigator, the deputy principal investigator, the study staff, as well as the hospital board member and the statistician were obtained (see original in German).

LITERATURE

1. Bialkowski W, Bryant BJ, Schlumpf KS, et al. The strategies to reduce iron deficiency in blood donors randomized trial: design, enrolment and early retention. Vox Sang. Feb 2015;108(2):178-185.
2. Finch CA, Cook JD, Labbe RF, Culala M. Effect of blood donation on iron stores as evaluated by serum ferritin. Blood. Sep 1977;50(3):441-447.
3. Cable RG, Glynn SA, Kiss JE, et al. Iron deficiency in blood donors: analysis of enrollment data from the REDS-II Donor Iron Status Evaluation (RISE) study. Transfusion. 2011;51(3):511-522.
4. Rigas AS, Sørensen CJ, Pedersen OB, et al. Predictors of iron levels in 14,737 Danish blood donors: results from the Danish Blood Donor Study. Transfusion. 2014;54(3pt2):789-796.
5. Conrad ME, Crosby WH, Jacobs A, Kaltwasser JP, Nusbacher J. The Hippocratian principle of 'primum nil nocere' demands that the metabolic state of a donor should be normalized prior to a subsequent donation of blood or plasma. How much blood, relative to his body weight, can a donor give over a certain period, without a continuous deviation of iron metabolism in the direction of iron deficiency? Vox Sang. Nov-Dec 1981;41(5-6):336-343.
6. Bianco C, Brittenham G, Gilcher RO, et al. Maintaining iron balance in women blood donors of childbearing age: summary of a workshop. Transfusion. Jun 2002;42(6):798-805.
7. Cable RG, Brambilla D, Glynn SA, et al. Effect of iron supplementation on iron stores and total body iron after whole blood donation. Transfusion. Aug 2016;56(8):2005-2012.

8. Nielsen P. Diagnostik und Therapie von Eisenmangel mit und ohne Anämie. Vol 2: UNI-MED Verlag AG, D-28323 Bremen; 2016:111.
9. Kiss JE, Brambilla D, Glynn SA, et al. Oral iron supplementation after blood donation: a randomized clinical trial. JAMA. Feb 10 2015;313(6):575-583.
10. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015.
11. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. The Lancet Haematology. 2017;4(11):e524-e533.
12. Pisani A, Riccio E, Sabbatini M, Andreucci M, Del Rio A, Visciano B. Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial. Nephrology dialysis transplantation. 2014;30(4):645-652.
13. Parisi F, Berti C, Mandò C, Martinelli A, Mazzali C, Cetin I. Effects of different regimens of iron prophylaxis on maternal iron status and pregnancy outcome: a randomized control trial. The Journal of Maternal-Fetal & Neonatal Medicine. 2017;30(15):1787-1792.
14. Spencer BR, Kleinman S, Wright DJ, et al. Restless legs syndrome, pica, and iron status in blood donors. Transfusion. 2013;53(8):1645-1652.
15. Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ. May 24 2003;326(7399):1124.
16. Brownlie IV T, Utermohlen V, Hinton PS, Haas JD. Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. Am. J. Clin. Nutr. Mar 2004;79(3):437-443.
17. Murray-Kolb LE, Beard JL. Iron treatment normalizes cognitive functioning in young women. Am. J. Clin. Nutr. Mar 2007;85(3):778-787.
18. Moeinvaziri M, Mansoori P, Holakooee K, Safaee Naraghi Z, Abbasi A. Iron status in diffuse telogen hair loss among women. Acta Dermatovenerologica Croatica. 2009;17(4):0-0.
19. Khan HMS, Sohail M, Ali A, Akhtar N, Khan H, Rasool F. Symptoms-Based Evaluation of Iron Deficiency Anemia in Students of Bahawalpur Correlated with their Eating Habits. Tropical Journal of Pharmaceutical Research. 2014;13(5):769-772.
20. Chansky MC, King MR, Bialkowski W, et al. Qualitative assessment of pica experienced by frequent blood donors. Transfusion. Feb 05 2017.
21. Angermeyer MC, Kilian R, Matschinger H. WHOQOL - 100 und WHOQOL - BREF: Handbuch für die deutschsprachige Version der WHO-Instrumente zur Erfassung von Lebensqualität. Hogrefe; 2000.
22. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol. Med. 1998;28(3):551-558.
23. Beutel M, Hinz A, Albani C, Brähler E. Fatigue assessment questionnaire: standardization of a cancer-specific instrument based on the general population. Oncology. 2006;70(5):351-357.
24. Glaus A, Müller S. Messung der Müdigkeit bei Krebskranken im Deutschen Sprachraum: Die Entwicklung des Fatigue Assessment Questionnaires. Pflege. 2001;14(3):161-170.
25. Crönlein T, Langguth B, Popp R, Lukesch H, Pieh C, Hajak G, Geisler P. Regensburg Insomnia Scale (RIS): a new short rating scale for the assessment of psychological symptoms and sleep in insomnia; Study design: development and validation of a new short self-rating scale in a sample of 218 patiens suffering from insomnia and 94 healthy controls. Health Qual. Life Outcomes 2013; 11:65.
26. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003;4(2):101-119.