STATISTICAL ANALYSIS PLAN

TRIAL FULL TITLE	Randomized study to compare HEMAX® PFS versus EPREX/ ERYPO® to Treat Anemia in pre-dialysis patients with Chronic Kidney Disease with Epoetin Alfa
SAP VERSION	Version 1.0
ClinicalTrials.gov Identifier	NCT04036253
PROTOCOL VERSION	Version 3.0 Argentina; 26 June 2018 (including Amendment v1.0, 10 July 2017 and Amendment v2.0 26 June 2018)
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2 Abbreviations and Definitions

AE	Adverse Event
ANCOVA	
ANMAT	Argentine National Administration for Drugs, Food, and Medical Devices
CKI	Chronic kidney insufficiency
CRF	Case Report Form
CVA	Cerebrovascular Accident
dl	DECILITER
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
g	Gram
Hb	Hemoglobin
HDL	High Density Lipoprotein
Hg	Mercury
IU	International Units
kg	Kilogram
LDL	Low Density Lipoprotein
LOCF	Last Observation Carry Forward
m2	Square meter
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary For Regulatory Authorities
min	minute
ml	mililiter
SAP	Statistical Analysis Plan
SPSS	Statistical Package for Social Sciences
“t”	Student test
TEAE	treatment - emergent adverse event
TIA	Transient Ischemic Attack

3 Introduction

3.1 Purpose of the analyses

These analyses will assess the efficacy and safety of HEMAX PFS® versus in comparison with EPREX/ ERYPO®.

3.2 Key Protocol Information

3.2.1 Study Objectives and Endpoints

3.2.2 Study Objectives

GENERAL OBJECTIVE

Evaluate the efficacy and safety of HEMAX PFS compared with EPREX/ERYPO®, following a dose titration and maintenance scheme similar to that used in the clinical practice in Argentina.

PRIMARY OBJECTIVE:

Evaluate the efficacy of treatment with epoetin alfa through increased levels of hemoglobin (Hb) from baseline value to the mean value of the 8 to 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

Evaluate the safety through the incidence of adverse events and adverse reactions after 12 and 24 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO.

SECUNDARY OBJECTIVES:

Evaluate the efficacy of treatment with epoetin alfa through the percentage of responder patients (increase of Hb ≥ 1g/ dl) after 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

Evaluate the percentage of transfusion requirement after 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

Evaluate the intragroup efficacy (HEMAX PFS and EPREX/ ERYPO®) of treatment with epoetin alfa through increased levels of hemoglobin from baseline in each one of the intermediate visits until the week 12 visit.

Evaluate the intragroup efficacy (HEMAX PFS and EPREX/ ERYPO®) of the change from the twice-a-week dosing during the titration phase to a weekly dosing during the maintenance phase through the variation of the hemoglobin levels from week 12 to weeks 16, 20 and 24.

In addition, at week 12 and 24 visits, an anti-erythropoietin antibody dosing will be performed to evaluate treatment immunogenicity..

EXPLORATORY OBJECTIVE

Evaluate the baseline value of hepcidin through ELISA at 12 and 24 weeks, in relation to treatment response.

3.2.3 Endpoints

EFFICACY EVALUATION

The following parameters will be evaluated for treatment efficacy, according to the objectives defined by the protocol at each visit:

- Levels of hemoglobin and its variation at each visit, with intragroup and intergroup comparison

The primary efficacy assessment will be carried out through the levels of hemoglobin increase from baseline value to the mean value of the visits between week 8 and 12, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

- Percentage of responder patients, defined as the increase of Hb ≥1g/ dl without transfusion requirement.

Percentage of responder patients (increase of Hb ≥ 1g/ dl) after 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

- Number and percentage of patients that require at least one transfusion.

Percentage of transfusion requirement after 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

- Intragroup efficacy of treatment with epoetin alfa

Increased levels of hemoglobin from baseline in each one of the intermediate visits until the week 12 visit.

- Intragroup efficacy of the change from the twice a week dosing during the titration phase to a weekly dosing during the maintenance phase.

Variation of the hemoglobin levels from week 12 to weeks 16, 20 and 24.

- Level of hepcidin at baseline, 12 and 24 weeks.

Relationship between the basal levels of hepcidin with the fall in filtrate and the hemoglobin level.

Response of hepcidin levels to treatment with erythropoietin

Association between hepcidin levels and the subgroup of patients who do not respond to erythropoietin.

SAFETY EVALUATION

• Adverse events:

Incidence of adverse events and adverse reactions will be evaluated after 12 and 24 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

In addition, and with focus on safety, the following will be discussed:

- Incidence of thromboembolic events (myocardial infarction, cerebrovascular accident, deep vein thrombosis and other thromboembolic events).
- Incidence of hypertension as TEAE.
- Blood pressure values at each visit.
- Complete baseline laboratory data and at week 12 and 24 visits,
- Antibody dosages, baseline and at weeks 12 and 24
- Vital signs: Determinations of pulse and blood pressure were recorded at every visit.
- Physical examination: A brief physical examination was carried out at the baseline visit (week 1).
- Electrocardiogram: An electrocardiogram was performed at the baseline visit (week 1).

3.2.4 Statistical Hypotheses

Treatment equivalence will be established if the difference between the two groups excludes a difference between treatment groups greater than 1g/ dl in hemoglobin increase from baseline value to the mean value of the visits between week 8 and 12 with a difference in the mean dose of epoetin alfa in these visits no greater than 20%.

The following equivalence statistical hypotheses is to be tested at a two-sided significance level of 5%:

- H0: Treatment difference in mean Hb during the primary efficacy evaluation period, between treatment arms (HEMAX PFS versus EPREX/ERYPO®), is within ±1.0 g/dL or less.
- H1: Treatment difference in mean Hb during the primary efficacy evaluation period, between treatment arms (HEMAX PFS versus EPREX/ERYPO®), is greater than ±1.0 g/dL.

Only when the primary endpoint achieves equivalence, statistical testing will progress to the secondary endpoints according to the stepdown procedure.

4 Study Methods

4.1 General Study Design and Plan

A multicenter, randomized open Phase IIB study to compare two epoetin alfa (HEMAX® PFS versus EPREX/ ERYPO®) is designed.

Pre-dialysis patients older than 18 years old with chronic kidney insufficiency (CKI), defined by glomerular filtration of ≥15 mL/ min/ 1.73 m2, and <60 mL/ min/ 1.73 m2 using the Modification of Diet in Renal Disease Study (MDRD) formula, with indication for treating anemia and hemoglobin levels <10.5 g/ dL, that had not received any previous treatment with erythropoietin stimulating agents 3 months before the study was initiated, were chosen.

Selected patients according to the inclusion and exclusion criteria were randomized in a ratio 1:1, stratified by gender to receive HEMAX® PFS or EPREX/ ERYPO® at an initial dose of 29 IU/ kg by subcutaneous route, twice a week (2000 IU, twice a week for 70 kg weight), to titrate according to the schedule detailed in Section 8.1 TREATMENTS ADMINISTERED. Patients´ follow-up was carried out for the dose-titration during the first 12 weeks, followed by 12 additional weeks of maintenance with visits every 4 weeks.

4.2 Selection (Inclusion-Exclusion) Criteria

INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for the study:

1) Patients between 18 and 85 years of age of both sexes.

2) IRC defined by the glomerular filtration rate through the MDRD formula that is ≥15 ml/ min and <60 ml/ min by 1.73 m2.

3) Anemia with indication of treatment and Hb lower than 10.5 g/ dl and greater than 7.5 g/ dl.

4) Patients who have both the will and the capacity to give informed consent in writing.

5) Women with at least 2 years of menopause or surgically sterile 6 months ago or of childbearing potential that have a negative pregnancy test during the baseline visit and are willing to receive an effective birth control method (diaphragm or prophylactic associated with a spermicide since at least 21 days before the first treatment; or intrauterine device in place for at least 3 months before the first dose of epoetin alfa: or hormonal birth control method, in pills, patch or implant, initiated at least 3 months before the first treatment).

EXCLUSION CRITERIA

Any of the following criteria exclude the patient from participating in the study:

1) Patient with scheduled entry to dialysis or kidney transplant in the next 6 months.

2) Transferrin saturation < 20%.

3) Cause of renal failure (as the secondary ones to autoimmune diseases) that in the opinion of the physician may affect the normal development of the Protocol.

4) Active bleeding or history of hemorrhage that has caused significant decrease of hematocrits in the last 30 days.

5) Uncontrolled hypertension (≥160 mm Hg systolic pressure and/ or ≥100mm Hg diastolic pressure with anti - hypertensive treatment).

6) Anemia due to another cause other than the kidney disease.

7) Transfusion in the last 3 months before the baseline or screening visit.

8) Treatment with an erythropoiesis stimulating agent in the 3 months prior to the baseline or screening visit.

9) Increased risk of thromboembolic disease: Previous history of arterial thromboembolism (CVA, TIA, Acute Coronary Syndrome or other) in the last 6 months or venous thrombosis in the last twelve months prior to the baseline visit; surgery in the last month prior to the baseline visit; prolonged standstill or orthopedic surgery scheduled in the next 6 months or any other factor which in the opinion of the investigator may increase the risk of thromboembolism in the patient.

10) Hematological disease, including myelodysplastic syndrome or a history of hematologic neoplasia or solid tumor in the last 5 years.

11) History of congestive heart failure.

12) Pregnancy or breast - feeding.

13) Refusal of patient to participate in the protocol or patients with a medical condition that the investigator considers significantly relevant to prevent their participation in the study.

4.3 Randomisation and Blinding

All patients were assigned to the corresponding treatment group by an electronic randomization software system, stratified by gender, and in blocks per center. The randomization system was defined in the electronic data collection system.

4.4 Study Variables

PROCEDURES - SITE VISITS	**V1 Screen**	**V2 Random**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11 or Final**
Study weeks	- 1	0	S2	S4	S6	S8	S10	S12	S16	S20	S24
INVESTIGATOR ACTIVITIES											
Obtain the informed consent in writing	X										
Evaluate the inclusion and exclusion	X	X									
Randomization		X									
Blood pregnancy test HCG beta subunit (only in women of childbearing potential)		X	X	X	X	X	X		X	X	
Medical history (with concomitant medication) and physical examination	X										

Blood pressure and pulse	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X										
Complete laboratory test (hemogram; hepatogram; blood glucose; renal function; ionogram; lipids; iron metabolism)	X							X			
Control laboratory test: hemogram			X	X	X	X	X		X	X	
Laboratory measurement of antibodies and hepcidin	X							X			X
Dosing and dose adjustment		X	X	X	X	X	X	X	X	X	
Administration of subcutaneous		X	X	X	X	X	X	X	X	X	
Delivery of medication and dosage record card		X	X	X	X	X	X	X	X	X	
Medication control and dose recording			X	X	X	X	X	X	X	X	X
AEs recording		X	X	X	X	X	X	X	X	X	X

Randomization Visit 2 (Week 0) will be scheduled a week after the baseline screening visit with a window of ± 3 days from the respective date.

The time-window for randomization visit is one week ± 3 days from screening visit.

The time-window for visits 3, 4, 5, 6, and 7 (weeks 2, 4, 6, 8 and 10) is two weeks ± 1 week. The time-window for visits 9, 10 and 11 (weeks 16, 20 and 24) is four weeks ± 1 week.

Adverse events will be recorded from the moment the patient signed the written informed consent, and they will be recorded all the study long. They will be reviewed and updated in each visit, and anytime the patient will be contacted by telephone

5 Sample Size

A total number of 120 patients (60 in each group) will allow, with 80% of power, to rule out a difference between treatment groups greater than 1g/ dl in hemoglobin increase from baseline value to the mean value of the visits between week 8 and 12.

The trial starting date was February 15th, 2017 and the first patient was included on February 21st, 2018 and the date in which the last patient reached the primary evaluation criterion was March 23rd, 2021. Since the study started, the recruiting rate was lower than that expected. Many participating centers included one single patient or no one. During the whole study, Biosidus made its best effort to support and accompany the recruitment in the centers. Furthermore, new centers were opened until a total of 16 centers in CABA and Buenos Aires Province were achieved. Besides, amendments to the protocol were performed to include a specialized center in Paraguay.

Since in March 2020, an emergency situation was decreed due to COVID-19 pandemic. On March 20th, 2020, the Argentine National Administration for Drugs, Food, and Medical Devices (ANMAT) issued a set of regulations and recommendations, in a document titled “Regulations and recommendations regarding clinical pharmacology studies during the COVID-19 pandemic”, in order to preserve the activities regarding the clinical pharmacology studies, protecting the safety and welfare of the study participants. As a consequence, and according to the clauses, Biosidus S.A. designed a risk mitigation plan (Annex 14.13), that was submitted to the Study Ethics Committees and to ANMAT.

Although the recruiting was not suspended, the health situation determined a reduction in the recruitment ratio. The interim analysis according to the obtained data showed, preliminary, that the results were those expected and allowed the conclusions of this report to be valid enough statistically, though the “n” was lower than that estimated at the beginning.

Considering that the studied population is a population at risk, and that the internal analysis gave consistent results, the recruitment was ended before achieving the 120-patient-target, and finally the study enrolled 43 patients (23 in HEMAX group, and 20 in Eprex/ Erypo® group)..

Thus, the population safety was considered as a priority, and, moreover, the integrity of the results, already collected, were kept.

6 General Considerations

6.1 Timing of Analyses

The final analysis will be performed after the last study patient completes the week 24 visit and the database is clean. This analysis will produce all the safety results, including immunogenicity, at week 24.

6.2 Analysis Populations

6.2.1 Per Protocol Population

- All subjects who received any study drug and who completed at least week 12 follow up visit to evaluate primery efficacy endpoint and who did not substantially deviate from the protocol.

6.2.2 Safety Population

- All subjects who received any study treatment

6.3 Missing Data

Para los datos faltantes de hemoglobina se utilizará el método de la última observación llevada hacia adelante (LOCF).

6.4 Interim Analyses

A first interim analysis will be performed after the last study patient completes the week 12 visit and the database is clean. This analysis will produce all the efficacy and safety results at week 12.

7 Summary of Study Data

All data will be listed, taking into account site, subject, treatment, and visit number. All summary tables will be structured with a column for each treatment and will be annotated with the total population size relevant to that table, including any missing observations

Descriptive statistics:

Continuous variables will be summarized using descriptive statistics: N, mean, standard deviation, median, minimum and maximum.

Categorical variables will be presented using frequencies and percentages

Inferential statistics

Inferential statistics will be performed through intergroup analysis using ANCOVA covariance analysis comparing each treatment group (patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®) or the statistical "t" Student test for independent samples considering 5% significance level can be used. An additional intragroup analysis evaluating the variations in hemoglobin (increase from baseline to the average of the visits between weeks 8 and 12) adjusted for the baseline value, using a significance level of 5% will be calculated.

7.1 Subject Disposition

Subject Disposition will be describe with a figure following CONSORT statement[1] including all the subjects enrolled, subjects that received recombinant human erythropoietin by treatment group (HEMAX® PFS or EPREX/ERYPO), withdrawn subjects and reason for withdrawal (such as Transfusion, Adverse Event, Lack of efficacy or withdrew consent).

7.2 Protocol Deviations

The study team throughout the conduct of the study will track all the protocol deviations and they will be notified to the Ethic Committees and/or regulatory authorities, either in immediate reports, or in the periodic reports if it is required. Risk for patient's safety will be evaluated for each deviation.

Major deviations which could result in exclusion from the per-protocol analysis population will also be summarized and listed. These deviations are:

- Eligibility Criteria Not Met
- Non-compliance with randomized medication and/or wrong study treatment or assignment administered before week 12
- Lack of evaluable Hb value corresponding to primary endpoint at week 12

7.3 Demographic and Baseline Variables

The following data will be collected and summarize: Sex (male/female, number and percentage) Age (years, median, and range) Weight (kg, mean ± SD) Height (m, mean ± SD) Body Mass Index (mean ±

SD), probable cause for kidney disease by treatment group (such as Diabetes, Arterial Hypertensión, Systemic Erythematous Lupus, other causes for nephritis, Para-infectious Glomerulopathy)

7.4 Concurrent Illnesses and Medical Conditions

The concurrent illnesses and medical conditions will be describe using MedDRA

7.5 Prior and Concurrent Medications

Prohibited Medications:

Transfusions: Patients will be transfused according to the clinical judgment of the investigator, based on the patient's symptoms and not on a cutoff value of hemoglobin. The transfused patients will be withdrawn from the study for having reached a study endpoint.

Permitted medications

Iron intake: All patients will receive concomitant treatment with iron orally to maintain the levels of transferrin saturation >20% according to the indications of the treating physicians. The intravenous iron is also permitted, according to the criterion of the treating physicians

Other data to be collected related to prior and concomitant medications are:

- Number of patients with anemia that had received treatments previously and number of treatments received previously by each patient
- Other concomitant medication administered to the randomized patients not specific for anemia (such as hypertension or diabetes).

7.6 Treatment Compliance

The patients should return to the center all the containers with the drug product used during the study, and all the medications that they had not used during the study. The staff in the center recorded in the source document and on the patient accountability individual record, the patient number, and the number of returned containers.

During the study, the monitor checked continuously all the containers with the study medication (used, and non-used containers), and the corresponding accountability forms. At the same time, at each visit the card in which the patient recorded the date and drug product dose administered, is checked. Accountability records of the drug products used during the study were kept in the centers all the time. At the moment the study was ended a final accountability was carried out and all the remnant medication was withdrawn for destruction, as stated in current regulations. .

The following measures will de obtained related to treatment compliance:

- Epoetin dose (IU) administered every week in each group (mean ± SD): Mean for cumulative doses per patient at the titration stage, maintenance stage, and during the whole treatment
- Number of patients that suspended the treatment at each visit

8 Efficacy Analyses

All efficacy variables will be listed by subject within study site. Data will be summarized by treatment group. Number and percentage will summarize categorical efficacy variables and Number, Mean, Standard Deviation, Minimum and Maximum will summarize continuous efficacy variables, whereas.

Inferential statistics will be performed through intergroup analysis analysis using ANCOVA covariance analysis comparing each treatment group (patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®) or the statistical "t" Student test for independent samples considering 5% significance level.

An additional intragroup analysis evaluating the variations in hemoglobin (increase from baseline to the average of the visits between weeks 8 and 12) adjusted for the baseline value, using a significance level of 5% will be performed

The assumptions regarding normality and homogeneity will be checked.

8.1 Primary Efficacy Analysis

The primary efficacy analysis will be performed for Per Protocol population.

The primary efficacy assessment will be carried out through the levels of hemoglobin increase from baseline value to the mean value of the visits between week 8 and 12, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

Additionally, treatment equivalence will be established if the difference between the two groups excludes a difference between treatment groups greater than 1g/ dl in hemoglobin increase from baseline value to the mean value of the visits between week 8 and 12 with a difference in the mean dose of epoetin alfa in these visits no greater than 20%.

8.2 Secondary Efficacy Analyses

- Percentage of responder patients (increase of Hb ≥ 1g/ dl) after 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.
- Percentage of transfusion requirement after 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.
- Intragroup efficacy (HEMAX PFS and EPREX/ ERYPO®) of treatment with Epoetin Alfa through increased levels of hemoglobin from baseline in each one of the intermediate visits until the week 12 visit.
- Evaluate the intragroup efficacy (HEMAX PFS and EPREX/ ERYPO®) of the change from the twice - a - week dosing during the titration phase to a weekly dosing during the maintenance phase through the variation of the hemoglobin levels from week 12 to the weeks 16, 20 and 24.

8.3 Exploratory Efficacy Analyses

The level of hepcidin at baseline, 12 and 24 weeks will be evaluated in relation to the response to treatment in order to observe the relationship between the basal levels of hepcidin with the fall in filtrate and the hemoglobin level. We will also observe the response of hepcidin levels to treatment with erythropoietin and finally we will see if there is any type of association between hepcidin levels and the subgroup of patients who do not respond to erythropoietin.

9 Safety Analyses

The following measures will be performed during the study to evaluate safety parameters:

- Vital signs: Determinations of pulse and blood pressure, every visit.
- Physical examination: A brief physical examination was carried out at the baseline visit (week 1).
- Electrocardiogram: An electrocardiogram was performed at the baseline visit (week 1).

Data will be summarized and comparison between treatment groups regarding these parameters at the beginning or at the end of the study will be evaluated.

9.1 Adverse Events

As safety objective, the incidence of adverse events and adverse reactions will be evaluated after 12 and 24 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®.

An AE shall be considered as treatment - emergent adverse event (TEAE), if it presents after the first dose administered of the investigational product or if, preexistent prior to the administration of the first dose, it worsens after the administration of the same.

All TEAEs will be presented summarized through the use of Tables, for each organ class and preferred term to denominate them. The Tables will present the number of patients for which events occurred, and the incidence rate, expressed as a percentage calculated on the number of patients from the entire population included in the safety FAS.

The TEAEs will be presented by causality (relationship with the study drug), intensity (mild, moderate, severe). Treatment - emergent events that are serious and that lead to treatment discontinuation will also be summarized using the preferred term and the class organ system involved.

In addition, and with focus on safety, the following will be discussed:

- Incidence of thromboembolic events (myocardial infarction, cerebrovascular accident, deep vein thrombosis and other thromboembolic events).
- Incidence of hypertension as TEAE.
- Blood pressure values at each visit.
- Complete baseline laboratory data and at week 12 and 24 visits,
- Antibody dosages, baseline and at weeks 12 and 24.

For safety analysis, descriptive statistics will be performed mainly to evaluate the incidence of adverse events and adverse reactions after 12 and 24 weeks of treatment.

When calculating the incidence of adverse events, or any sub-classification (e.g. by treatment) each subject will be counted all the times a repetitions of adverse events will be occurred and the denominator will be the total population size.

All the adverse events occurred during the study will be listed according to treatment group and severity. The frequency of adverse events by system and treatment group, expressed as amount of events/number of affected patients and the relationship with study drug will be summarized.

9.2 Deaths, Serious Adverse Events and other Significant Adverse Events

All the serious adverse events will be recorded. The relationship with study drug will be summarized

9.3 Pregnancies

Pregnancy reports will be sent to Biosidus S.A. so as to be included in the safety database. This requirement includes the normal pregnancies without AEs.

A pregnancy follow-up must be made in order to determine pregnancy results, including spontaneous or voluntary interruption, the birth details, the presence or absence of any birth defect, congenital anomalies or complications in the mother or in the newborn. The pregnancy follow-up report should be registered in the specific eCRF.

9.4 Clinical Laboratory Evaluations

For the assessment of safety, the determination of complete laboratory parameters will be determined in the baseline visit, and during visits weeks 12 and 24, or at the end of the study, in which the following parameters will be tested:

- Liver function tests,
- Glycemia, lipid profile (HDL, LDL, and triglycerides),
- Ionogram, calcium, phosphorus, urea, and creatinine, and
- Sideremia (serum iron), transferrin and its saturation, and ferritin

The values of these parameters will be evaluated and summarizes by treatment group as if within the normal range or out of range. In this case, clinical significance will be provided, as clinically significant or not clinically significant. .

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10 Quality Control

The investigator, study coordinator, or other study staff, duly trained and appointed, performed the data entry in the center. The eCRFs were completed for each recruited patient according to the patient source data at each visit.

Patients were not identified by name. An appropriate coded identification was used; so that the patient could not be identified. The center investigator kept separately a form with the patient´s name, the non-identifiable initials and the patient´s address (i.e., an identification patient form).

The center investigator checked that each CRF was duly completed at each visit, and the clinical studies monitor confronted them with the source documents. The monitor and staff from Data Management department (DM) monitored each entry.
Integrity and internal consistency of data introduced in the study database were controlled during the monitor visit, versus the patient´s clinical history as source document. Deviations from these pre-defined and computerized validations arouse incoherencies in the database that were solved using the data correction form.

There are 2 mainly type of discrepancies:

- Automatic discrepancies, automatically generated during the data entry or following the data logical execution.

- Manual discrepancies, which a system user may generate at any time.

The investigator and his/her team were responsible for solving any data discrepancy in time and shape. Study monitors carried out the follow-up to confirm that the discrepancies had been solved.

The population to be used in a table or figure will be explicitly set at the start of a block of code that computes the output.

11 Technical Details

The randomization system was defined in the electronic data collection system. provided by the company Semicrol® S.L., Santander, Spain.

The Sponsor chose an electronic data capture (EDC) system (electronic CRF). The company Semicrol® (Santander, Spain) provided the service. The Sponsor granted Access to the system to all the PIs and to all the staff selected.

Statistical analysis will be performed with SPSS (Statistical Package for Social Sciences) software[2] or equivalent, such as the R Core Team Program (2020)[3]

12 Summary of Changes to the Protocol

Two general amendments, that were applicable to all the participating centers, were made.

Amendment #1 added two additional dosage forms of the study product (pre-filled syringes x 1000 and 3000 IU) and introduced some changes at the requirement of one of the Ethics Committees, which had been extended to all the centers. These modifications included a change regarding the Pregnancy tests in urine by the HCG beta sub-unit determination in blood, additional information about statistical tests and the descriptive statistics to be used, among others, were also included.

Amendment #2 added Paraguay and Uruguay as countries that might take part of the study, potentially.

13 References

[1] Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010 Jun 1;152(11):726-32. doi: 10.7326/0003-4819-152-11-201006010-00232. Epub 2010 Mar 24. PMID: 20335313.

[2] IBM SPSS version 25.0

[3] R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.