BIO SIDUS ARGENTINA S.A.

CLINICAL STUDY PROTOCOL

Study title:	**A Randomized, Comparative Study of HEMAX PFS® versus EPREX/ ERYPO® in the Treatment of Anemia with Epoetin Alfa in Patients with Predialysis Chronic Kidney Disease**
Protocol N°:	**BIOS - HPFS - 0115 (Study of HEMAX PFS VS EPREX/ ERYPO® in Predialysis Chronic Kidney Disease)**
Clinical phase:	**Phase IIIB**
Protocol version and date:	***Versión 3.0_Argentina; 26-Junio-2018*** **Includes General Amendment v1.0, 10-Julio-17** **Includes General Amendment v2.0, 26-Junio-2018**
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This clinical study will be conducted in accordance with the current Good Clinical Practice (GCP) guidelines, and the relevant ICH (International Conference on Harmonization) guidelines.

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The information contained in this document is considered privileged and confidential and may not be disclosed to third parties except to the extent necessary to achieve the approval from the Institutional Review Committees/ Ethics Committees, the informed consent and the regulatory authorities.

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2 SYNOPSIS

Protocol number	BIOS - HPFS - 0115
Study title	A Randomized, Comparative Study of HEMAX PFS® versus EPREX/ ERYPO® in the Treatment of Anemia with Epoetin Alfa in Patients with Predialysis Chronic Kidney Disease
Site number	Multicentric. Argentina, Paraguay and Uruguay. The list of Principal Investigators and the centers' data can be found in Annex 01.
Clinical phase	IIIB
Treatment duration	24 weeks (12 weeks of dose titration and 12 weeks of dose maintenance).
Study population	Patients with predialysis chronic renal failure (CRF) with indication of treatment of anemia and levels of hemoglobin < 10.5 g/ dl that have not received previous treatment in the past three months with an erythropoiesis stimulating agent.
Study objectives	Primary objectives: 1- Evaluate the efficacy of treatment with epoetin alfa through increased levels of hemoglobin 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®. 2- 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®. Secondary objectives: 1 - 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®. 2- Evaluate the percentage of transfusion requirement after 12 weeks of treatment, comparing patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®. 3- 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. 4- 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

	5- In addition, at week 12 and 24 visits, an anti - erythropoietin alfa antibody dosing will be performed to evaluate treatment immunogenicity. 6- In an exploratory way, the baseline value of hepcidin will be analyzed through ELISA at week 12 and 24, in relation to treatment response.
Study design	This is a multicenter, open - label, randomized and comparative phase IIIB study of two epoetins alfa (HEMAX PFS versus EPREX/ ERYPO®). Patients older than 18 years with predialysis chronic renal failure (CRF) defined by a glomerular filtration rate (calculated through the Modification of Diet in Renal Disease Study formula) that is ≥15 ml/ min by 1.73m2 and <60 ml/ min by 1.73 m2, with an indication of treatment of anemia and levels of hemoglobin <10.5 g/ dl, which have not received prior treatment with an erythropoiesis stimulating agent in the last 3 months. The patients that meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio with stratification by gender to receive HEMAX PFS or EPREX/ ERYPO® subcutaneously with an initial dose of 29 IU/ kg twice a week (2000 IU twice a week for 70 kg of weight), to be titrated according to the scheme that is summarized below. There will be a follow - up of patients with visits to the site every two weeks during the first 12 weeks of dose titration that will be followed by 12 additional weeks of dose maintenance with visits every 4 weeks. Usual titration scheme and dose management during the titration phase: • If the hemoglobin in any visit increases >1g/ dl in any period of 2 weeks prior to the visit, the dose will be reduced by 25%. • If the hemoglobin, in any visit, increases to values equal to or greater than 11.5 g/ dl the dose will be interrupted and resumed when the hemoglobin drops below 10.5 g/ dl, with a dose decrease by 25%. Only every four weeks (weeks 4 and 8) from treatment initiation during the titration period, the dose may be increased according to the following scheme: • If after four or eight weeks, hemoglobin does not increase by at least 1 g/ dl as compared to the baseline value, the dose will be increased by 25%. • If after twelve weeks, hemoglobin did not increase during the titration phase at any time at least 1 g/ dl as compared to

	Maintenance phase: Patients who have experienced during the titration phase an increase of the Hb of at least 1 g/ dl as compared to the baseline value, will enter the maintenance phase after week 12 until week 24, with visits every 4 weeks. All patients will be switched to a weekly dosing scheme in which they will receive the same total dose of epoetin alfa administered at the end of the titration phase (for example the patients who at the end of the titration phase are with 2000 IU twice a week, will receive 4000 IU weekly during the maintenance phase). During the maintenance phase, the following medication adjustments may be performed: • During the maintenance phase, despite receiving the indicated dose of epoetin alfa, if the Hb drops below 10.5 g/ dl, the dose may be adjusted by 25%. • If the hemoglobin, in any visit, increases to values equal to or greater than 11.5 g/ dl the dose will be interrupted and resumed when the hemoglobin drops below 10.5 g/ dl, with a dose decrease by 25%.
Patient number	There are plans to recruit 120 patients in total that will be randomized in a 1:1 ratio to receive HEMAX PFS (n: 60) or EPREX/ ERYPO® (n: 60).
Inclusion/ exclusion criteria	**Inclusion criteria** Patients must meet all of the following inclusion criteria to be eligible for the study: • Patients between 18 and 85 years of age of both sexes. • IRC defined by the glomerular filtration rate through the Modification of Diet in Renal Disease Study (MDRD) formula that is ≥15 ml/ min and <60 ml/ min by 1.73m2. • Anemia with indication of treatment and hemoglobin lower than 10.5 g/ dl and greater than 7.5 g/ dl. • Patients who have both the will and the capacity to give informed consent in writing. • 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. **Exclusion criteria** Any of the following criteria exclude the patient from participating in the study: • Patient with scheduled entry to dialysis or kidney transplant in the next 6 months. • Transferrin saturation < 20%

	• 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. • Active bleeding or history of hemorrhage that has caused significant decrease of hematocrits in the last 30 days. • Uncontrolled hypertension (≥160 mm Hg systolic pressure and/ or ≥100mm Hg diastolic pressure with anti - hypertensive treatment). • Anemia due to another cause other than the kidney disease. • Transfusion in the last 3 months before the baseline or screening visit. • Treatment with an erythropoiesis stimulating agent in the 3 months prior to the baseline or screening visit. • 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. • Hematological disease or myelodysplastic syndrome or a history of hematologic malignancy or solid tumor in the last 5 years. • History of congestive heart failure. • Pregnancy or breast - feeding. • Refusal of patient to participate in the protocol or patients
Route of administration and investigational product dosage	HEMAX PFS or EPREX/ ERYPO® (both epoetin alfa) at an initial dose of 29 IU/ kg twice a week subcutaneously (2000 IU twice a week for 70 kg of weight) during the 12 weeks of titration, followed by an equivalent weekly dose during the additional 12 weeks of maintenance.
Concomitant treatment of anemia	**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. **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

Statistical methods	**Sample size** A total 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. **Efficacy evaluations** The primary evaluation of efficacy will be carried out through the increased levels of hemoglobin 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 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 ≤20% in the mean dose of epoetin alfa in these visits. The secondary evaluation of efficacy will be carried out through the evaluation of the following objectives: • 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 transfusional 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 hemoglobin levels from week 12 to the weeks 16, 20 and 24. For missing hemoglobin data, the last observation carried forward

	Safety evaluations The safety evaluation to be carried out for the treatment cohort will include: Incidence, severity and seriousness of adverse events and adverse reactions including thromboembolic events, arterial hypertension, safety laboratory and other adverse events at 12 and 24 weeks of treatment. Dosing of anti - erythropoietin antibodies will be performed to evaluate the treatment immunogenicity in the baseline visit and in week 12 and 24 visits. **Data analysis and results:** There will be two formal database analyses. **A first analysis w**ill 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. **A second analysis** will be performed after the last study patient

3 LIST OF ABBREVIATIONS

TERM	DESCRIPTION
%	percentage
CVA	cerebrovascular accident
TIA	transitional ischemic accident
DNA	deoxyribonucleic acid
ANMAT	National Administration of Drugs, Food and Medical Devices
RA	regulatory authority
IECs	independent ethics committee
IECR	Institutional Ethics Committee for Research
CKD	chronic kidney disease
CRO	contract research organization
dl	deciliter
DM	data management
AE	adverse event
SAE	serious adverse event
ESA	erythropoiesis stimulating agent
ICRF	individual clinical record form
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	hemoglobin
HCG	human chorionic gonadotropin
HR	hazard ratio or risk ratio
ICH	International Conference on Harmonization
IRB	Institutional Review Board
CRF	chronic renal failure
MDRD	Modification of Diet in Renal Disease formula
mg	milligram
ml	milliliter
SC	subcutaneous
TEAE	treatment - emergent adverse events

4 INTRODUCTION

4.1 CHRONIC KIDNEY DISEASE AND ANEMIA

Chronic kidney disease (CKD) is associated with anemia due mainly to the decline of erythropoiesis by deficit of erythropoietin and, potentially, to secondary alterations in oxygen level[1]. The APREDIA study conducted in our country in predialysis population of patients with glomerular filtrate levels < 44.4 ml/ min, showed that 72% of the patients had values of hemoglobin (Hb) compatible with anemia and that this percentage increases to the extent that the deterioration of the renal function is greater[2].

The anemia in chronic kidney disease and its lack of treatment is associated with increased comorbidity, complications, cardiovascular risk, progression of kidney disease and decreased survival [3 - 8]. In addition, the treatment impacts favorably on the exercise capacity and the quality of life of patients [9 - 10]. In turn, the decrease in the transfusional requirement favorably impacts on the reduction of secondary complications to infectious diseases transmissible by blood transfusion, hemosiderosis and allosensibilization that may potentially adversely impact on a future kidney transplant[1].

4.2 TREATMENT WITH ERITROPYESIS STIMULATING AGENTS

Since its advent at the end of the '80s, recombinant erythropoietin became a pillar of the treatment of anemia in patients with chronic renal failure[1].
Large - scale controlled studies in patients with anemia and CKD have established an alert as to what is the level of hemoglobin and the ideal dose of erythropoiesis stimulating agents (ESA).

In these controlled clinical studies, when comparing the target higher levels of Hb (13 - 14 g/ dl) with the lower levels (9 - 11.3 g/ dl), it was noted that by titrating ESAs to the highest levels of hemoglobin, an increased risk of mortality, myocardial infarction, cerebrovascular accident, heart failure and other thromboembolic events[11 - 13] were obtained, as seen in the table shown below in this section.

In addition, the use of ESAs in other populations, such as cancer patients with curable tumors and anemia induced by chemotherapy or patients undergoing orthopedic surgery or coronary revascularization surgery, demonstrated the possibility of several problems, including in some cases increased mortality, increased risk of tumor progression or recurrence and thromboembolic events, so the use of ESA in some of these indications[1] is not recommended.

Study	Normal Hematocrit Study (NHS)[11]	CHOIR[12] (N = 1432)	TREAT[13] (N = 4038)
Population	CKD on dialysis with coronary heart disease or heart failure	CKD Not on dialysis with Hb < 11 g/ dL	CKD Not on dialysis with diabetes type II and Hb ≤ 11 g/ dL
ESA	Epoetin Alfa	Epoetin Alfa	Darbepoetin Alfa
Target Hb (in g/ dl)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median Hb (quartile 1	12.6 (11.6; 13.3)	13.0 (12.2; 13.4)	12.5 (12.0; 12.8)
Results	Increased mortality HR=1.27; 95% CI (1.04, 1.54);	Increase in major cardiovascular events (death, infarction, CVA or hospitalization due to heart	Increased CVA HR 1.92; 95% CI: (1.38, 2.68)

Based on this evidence, the current guidelines for the management of anemia in patients with CKD recommend treatment initiation with ESAs in the following cases[1]:

1.3.1 Patients with clinical individualized treatment indication (symptoms, decreased hemoglobin, risk of transfusion and inadequate response to the iron) with levels of hemoglobin <10 g/ dl. In patients with Hb levels >10 g/ dl the decision of treatment initiation must be individualized according to the potential risk/ benefit balance.

2.3.1 During treatment, the levels of Hb 11.5 g/ dl should not be exceeded.

3.3.1 Use the minimum necessary doses to maintain the Hb in the ranges described.

4.3 EPOETINA ALFA (HEMAX AND HEMAX PFS)

HEMAX® is a medication that contains epoetin alfa (human recombinant erythropoietin) as active pharmaceutical ingredient[14]. Epoetin is a glycoprotein of 165 amino acids produced by recombinant DNA technology, obtained from a genetically modified mammal cell line. Epoetin has a peak level of purity and is indistinguishable from natural human erythropoietin.

Erythropoietin induces the erythropoiesis by inhibiting apoptosis and stimulating the division and differentiation of erythropoietic stem cells in bone marrow, which results in an increase in the red blood cell volume and, consequently, the hematocrit. Erythropoietin also induces the release of reticulocytes from the bone marrow towards the bloodstream, where they mature to erythrocytes.
The normal concentration of endogenous erythropoietin is 10 - 30 mU/ ml and is influenced by the levels of oxygen to tissue level. When tissue oxygen levels decrease, the concentration of erythropoietin increases between 100 and
1,000 times This situation can also be seen in the patients with anemia.
Epoetin alfa, drug substance of HEMAX®, is administered parenterally (subcutaneous or intravenous). The initial increase in reticulocyte count occurs within 7 to 10 days after the administration. Clinically significant increases were found in the red blood cell, hematocrit and hemoglobin count, usually in 2 to 6 weeks after the administration of epoetin alfa. The range and extent of the response depends on the dose and on the availability of iron reserves.
The peak plasma concentration is achieved after 15 minutes following a single intravenous dose and between 5 to 24 hours following administration of a single dose subcutaneously. In the latter case, peak concentrations can be maintained for 12 to 16 hours and present detectable amounts for at least 24 hours following administration.
The half - life of epoetin alfa is 4 to 13 hours following intravenous or subcutaneous administration. The elimination half - life is generally higher following the first dose after two or more weeks of treatment. In general, after 24 h plasma levels of erythropoietin return to their baseline level. Following subcutaneous administration of epoetin, the peak concentration of the drug was observed between 5 and 24 hours after administration, and its decline is slower.
In studies conducted in healthy adult volunteers, it was observed that the half - life following intravenous administration of epoetin is 20 % lower in patients with renal failure. Furthermore, in a study conducted in healthy volunteers, it was noted that the half - life of HEMAX® administered subcutaneously was 20.8 ± 6.3 hours.
Once treatment is interrupted, the hematocrit may begin to decrease after 2 weeks.
The experience with HEMAX® in Argentina is more than 20 years, being one of the most widely used products in the treatment of anemia in patients with chronic kidney disease.

On the other hand, HEMAX PFS is a medication that also contains epoetin alfa (human recombinant erythropoietin) as active pharmaceutical ingredient (the same content in HEMAX®, differing in the primary packaging and mainly, in that it does not contain human albumin as an excipient[15], which is usually perceived as an improvement. The lack of albumin, that is a hemoderivative, decreases the risk of hypersensitivity reactions in patients who are allergic to albumin or to similar products derived from human blood and reduce the chance of infections transmissible through blood.

All studies conducted with HEMAX PFS® in the comparability exercise with the innovative epoetin alfa product have shown that both are biosimilar (Registration Dossier of Hemax PFS submitted to ANMAT, dossier n° 1 - 47 - 1110 - 793 - 14 - 6). Given that the drug active pharmaceutical ingredient is the same, any kind of difference between this formulation and the current formulation with albumin

(HEMAX®) is not expected. Given that the registration dossier of the new formulation (which was submitted at the end of 2014 but still has not been approved for marketing), this study is considered Phase IIIB and not Phase IV for the time being.

4.4 EPOETINA ALFA (EPREX/ ERYPO®)

EPREX® and ERYPO® are tradenames for a same medication that also contains epoetin alfa, obtained from a genetically modified mammal cell line[16]. EPREX/ ERYPO® are products with epoetin alfa developed by Janssen Cilag, in Belgium, which have been approved there by the local authority and by the ANMAT in our country (re - certification 3107 / 2011), being frequently used as an international reference product.

5 CURRENT STUDY RATIONALE

In order to obtain more scientific evidence on the use of epoetin alfa in the context of the current treatment of anemia in patients with predialysis CKD, it is of interest to perform a randomized study of HEMAX® controlled with a reference medication such as EPREX/ ERYPO®.

Based on this context and to conform to the current recommendations, we designed a study that will include patients with clinical indication for treatment and levels of hemoglobin <10.5 g/ dl with dose adjustment in aliquots of 25% and interruption of treatment if the Hb reaches values equal to or greater than 11.5 g/ dl so as to maintain the hemoglobin concentration between 10.4 and 11.4g/ dl. Patients with increased thromboembolic risk will be excluded from the study.

The initial dose of epoetin alfa currently recommended for treatment initiation in patients with predialysis CKD are 50 - 100 IU/ kg three times a week subcutaneously. However, these doses are not the ones used in the usual clinical practice in our country, where treatment is initiated with lower doses of 20 to 40 IU/ kg twice a week. This therapeutic approach has the advantage of being more in line with the current recommendations, exposing the patient to lower initial doses, in addition to the convenience to the patient of administering the medication only twice a week instead of three times a week. In addition, it is frequent during the maintenance phase or even from the start to administer epoetin in a single weekly dose. This dosing scheme is founded on that the clinically relevant pharmacodynamic effect of epoetin alfa does not depend on its plasma half - life but on the half - life of the red blood cells. Several clinical studies have demonstrated the equivalence and safety of epoetin administration schemes weekly, every two weeks and every 3 weeks[17 - 23].

It is interesting to note that the mean weekly dose of epoetin alfa used in more recent studies has been 5000 ± 2500 IU/ week, a dose that is in the range of our initial dose[24].

For these reasons, our study will use a scheme that is frequently used in the practice in our country using lower initial doses administered twice a week subcutaneously in the initial titration phase of 12 weeks, switching then to the same weekly dose but administered once a week during the maintenance phase. Thus, local additional evidence on the efficacy and safety of this dosing scheme will be obtained.

6 STUDY OBJECTIVES

The study has as a general objective the evaluation of 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 our country, being the specific objectives the following.

6.1 PRIMARY OBJECTIVES:

Evaluate the efficacy of treatment with epoetin alfa through increased levels of hemoglobin 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®.

6.2 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 week12 and 24 visits, an anti - erythropoietin antibody dosing will be performed to evaluate treatment immunogenicity.

6.3 EXPLORATORY OBJECTIVE

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

7 LABORATORIES

Hemoglobin levels will be analyzed at each center's local laboratory.
Anti-erythropoietin antibodies and hepcidin level will be analyzed at BIOSIDUS S.A. located at Constitución N°4216/24/34, Mármol N°1213/23 and Tarija N°4243/45/51/57/63, Ciudad Autónoma de Buenos Aires.

8 STUDY DESIGN

This is a multicenter, open - label, randomized and comparative phase IIIB study of two epoetins alfa (HEMAX PFS versus EPREX/ ERYPO®).
Patients older than 18 years with predialysis chronic renal failure (CRF) defined by a glomerular filtration rate through the Modification of Diet in Renal Disease Study formula that is ≥15 ml/ min by 1.73 m_2 and <60 ml/ min by 1.73 m_2, with an indication of treatment of anemia and levels of hemoglobin <10.5 g/ dl, which have not received prior treatment with an erythropoiesis stimulating agent in the last 3 months.
The patients that meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio with stratification by gender to receive HEMAX® PFS or EPREX/ ERYPO® subcutaneously with an initial dose of 29 IU/ kg twice a week (2000 IU twice a week for 70 kg of weight), to be titrated according to the scheme that is summarized in Section 7.
There will be a follow - up of patients with visits to the site every two weeks during the first 12 weeks of dose titration that will be followed by 12 additional weeks of dose maintenance with visits every 4 weeks.

9 STUDY POPULATION

Patients with kidney disease and predialysis chronic renal failure (CRF) with indication of treatment of anemia and levels of hemoglobin < 10.5 g/ dl that have not received previous treatment in the past three months with an erythropoiesis stimulating agent.

9.1 PATIENT NUMBER

There are plans to recruit 120 patients in total that will be randomized in a 1:1 ratio to receive HEMAX PFS (n = 60) or EPREX/ ERYPO® (n = 60).

9.2 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 Modification of Diet in Renal Disease Study (MDRD) formula that is ≥15 ml/ min and <60 ml/ min by 1.73 m_2.
3) Anemia with indication of treatment and hemoglobin 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).

9.3 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.

9.4 EARLY TREATMENT TERMINATION

The termination visit should be performed in all patients that completed the study prematurely. Patients who decide not to continue with the visits must perform the termination visit before completion. A patient may leave or be excluded from the study due to the following reasons:

- Death.
- Adverse event that in the opinion of the investigator requires early withdrawal (specify principal AE in the AE form).
- Revocation of informed consent.
- At the request of the investigator or physician primarily responsible for the care of the patient.
- Due to major protocol violation that required discontinuation.
- Loss of follow - up, including the fact that patient does not return to the site.
- Positive pregnancy test at any time during the study.
- Patient transfusion or lack of response after 12 weeks of treatment.
- If after twelve weeks the hemoglobin did not increase during the titration phase by at least 1 g/dL from baseline, the patient will be withdrawn from the study.

10 MEDICATIONS/ TREATMENT AND CONCOMITANT MEDICATIONS

10.1 MEDICATION/ TREATMENT

HEMAX PFS or EPREX/ ERYPO® (both epoetin alfa) at an initial dose of 29 IU/ kg twice a week

subcutaneously (2000 IU twice a week for 70 kg of weight) during the 12 weeks of titration, followed by an equivalent weekly dose during the additional 12 weeks of maintenance.

Usual titration scheme and dose management during the titration phase:

- If the hemoglobin in any visit increases >1 g/ dl in any period of 2 weeks prior to the visit, the dose will be reduced by 25%.
- If the hemoglobin, in any visit, increases to values equal to or greater than 11.5 g/ dl the dose will be interrupted and resumed when the hemoglobin drops below 10.5 g/ dl, with a dose decrease by 25%.

Only every four weeks (weeks 4 and 8) from treatment initiation and during the titration period, the dose may be increased according to the following scheme:

- If after four or eight weeks, hemoglobin does not increase by at least 1 g/ dl as compared to the baseline value, the dose will be increased by 25%.
- If after twelve weeks, hemoglobin did not increase during the titration phase at least 1 g/ dl as compared to the baseline value, the patient will be withdrawn from the study.

Maintenance phase:

Patients who have experienced during the titration phase an increase of the Hb of at least 1 g/ dl as compared to the baseline value, will enter the maintenance phase after week 12 until week 24, with visits every 4 weeks. All patients will be switched to a weekly dosing scheme in which they will receive the same total dose of epoetin alfa administered at the end of the titration phase (for example the patients who at the end of the titration phase are with 2000 IU twice a week will receive 4000 IU weekly during the maintenance phase). During the maintenance phase, the following medication adjustments may be performed:

- If despite receiving the indicated dose of epoetin alfa, the Hb drops below 10.5 g/ dl, the dose may be adjusted by 25%.
- If the hemoglobin, in any visit, increases to values equal to or greater than 11.5 g/ dl, the dose will be interrupted and resumed when the hemoglobin has dropped below 10.5 g/ dl, with a dose decrease by 25%.

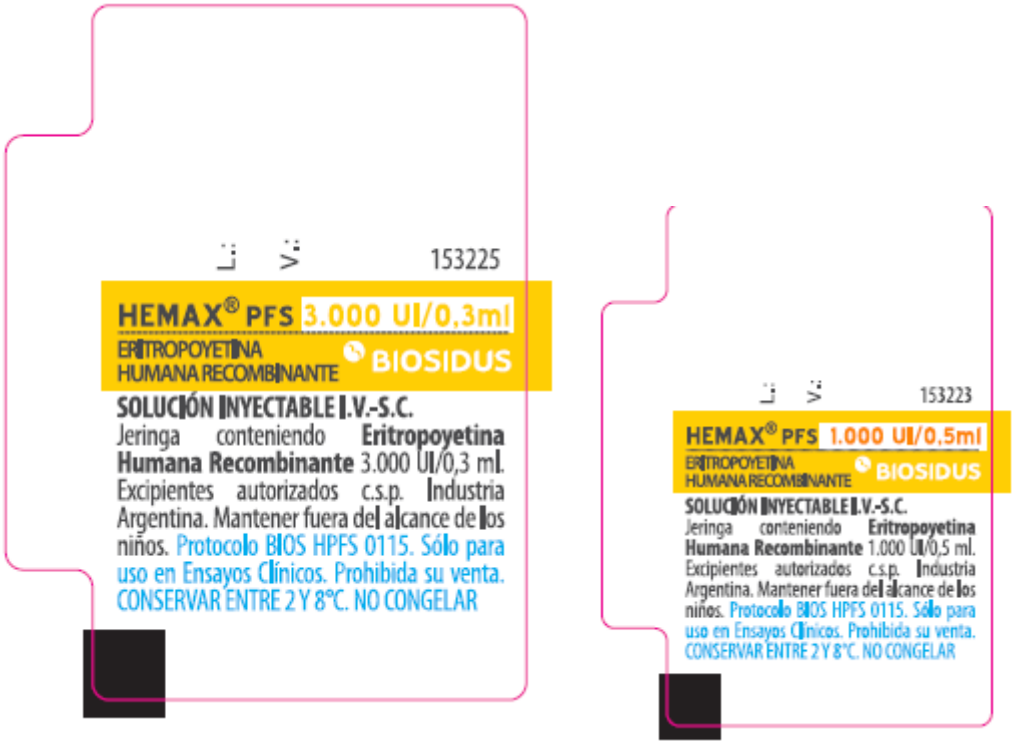
Application of Medication:

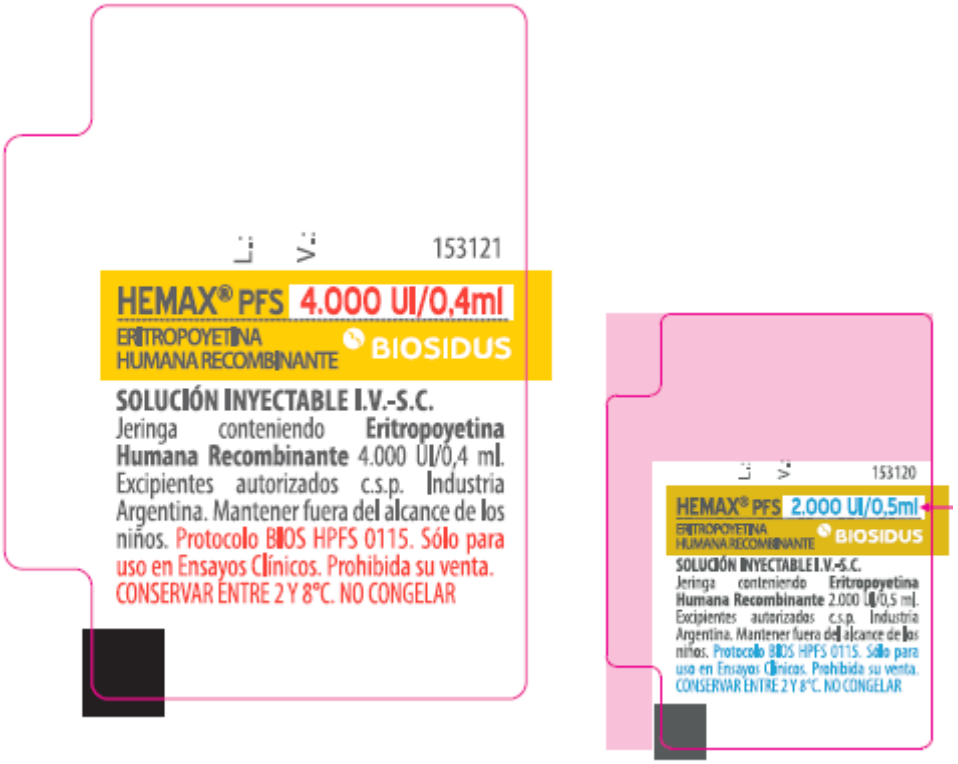
According to the above titration scheme the different medication presentations described in section 9.5 will be used to facilitate application and avoid risks related to potential overdosing. During the titration phase, responder patients (hemoglobin increases greater than 1 g/dL) who require a dose reduction may receive the reduced dose in a single weekly application in order to facilitate application and avoid the

potential risks of overdosage. In the (rare) cases in which the patient has sustained hemoglobin increases greater than 1 g/dL and requires doses less than 1000IU/week, the dose will be suspended and restarted at 1000IU/week when the hemoglobin is < 10.5 g/dL to avoid the potential risk of overdosing in responders.

11 STUDY MEDICATION LABELING

11.1 PRIMARY PACKAGING





11.2 SECONDARY PACKAGING

EPREX®/ERYPO® UI/ ml
ERITROPOYETINA HUMANA RECOMBINANTE
Solución Inyectable I.V.-S.C.
Jeringa conteniendo Eritropoyetina Humana Recombinante 1.000 UI/0,5 ml. Excipientes autorizados c.s.p. Industria Holandesa.
Mantener fuera del alcance de los niños.
Sólo Uso Ensayos Clínicos. Prohibida su venta.
CONSERVAR ENTRE 2 Y 8ºC. NO CONGELAR
Investigador: _____
Nº de Paciente: _____
Janssen-Cilag,1 rue Camille Desmoulins, TSA 91003 – 92787 Issy – Les Moulineaux Cedex 9, Francia
Lote: Vencimiento:

HEMAX®PFS UI/ ml
ERITROPOYETINA HUMANA RECOMBINANTE
Solución Inyectable I.V.-S.C.
Jeringa conteniendo Eritropoyetina Humana Recombinante 2.000 UI/0,5 ml. Excipientes autorizados c.s.p. Industria Argentina.
Mantener fuera del alcance de los niños.
Sólo Uso Ensayos Clínicos. Prohibida su venta.
CONSERVAR ENTRE 2 Y 8ºC. NO CONGELAR
Investigador: _____
N° de Paciente: _____
BIOSIDUS SA, Constitución 4234, CABA
Sólo Uso Ensayos Clínicos. Prohibida su venta.
Lote: Vencimiento:

11.3 CONCOMITANT MEDICATIONS/ TREATMENT OF ANEMIA

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.

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.

12 STUDY DEVELOPMENT

12.1 STUDY PROCEDURES

This study will include a screening or baseline visit (a week before randomization), a randomization visit (week 0), a treatment titration phase (week 0 to week 12) and a maintenance period (between week 12 and 24). The visit windows are ± 7 days post - randomization. In the table below, there is a detailed summary of the activities.

12.2 STUDY PROCEDURE TABLES

PROCEDURES - SITE VISITS	V1 Scree	V2 Rando	V3	V	V5	V	V7	V	V9	V10	V11 or
Study weeks	-	0	S2	S	S6	S	S10	S1	S1	S20	S24
INVESTIGATOR ACTIVITIES											
Obtain the informed consent in writing	X										

Evaluate the inclusion and exclusion criteria	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 medication		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

12.3 DETAILED STUDY PLAN

12.3.1 Baseline evaluation visit 1 (week -1)

Before performing any study procedure/ evaluation, the patient must have been duly informed on all aspects of the study, including scheduled visits and activities and must sign an informed consent. The patient will be given a signed copy of the informed consent.
The following tasks will be carried out during the baseline visit:

- Review and sign the informed consent with delivery of a signed copy for the patient.
- Evaluate the inclusion and exclusion criteria.
- Samples for full local laboratory test, consisting of:
  - Complete hemogram with reticulocyte (through cytometry or automatic counter) and platelet count.
  - Hepatogram,
  - Glycemia, lipid profile (HDL, LDL and triglycerides)

- Ionogram, calcium, phosphorus, urea and creatinine,
- Serum iron, transferrin, transferrin saturation, and ferritin
- Beta subunit of chorionic gonadotropin only in women of childbearing potential
- Serum sample for antibodies and hepcidin dosage (the sample will be collected and an aliquot will be stored at - 20º C for further analysis)

- Medical history (with concomitant medication) and a physical examination (with weight and height), registering only the clinically relevant findings.
- Pulse: the radial pulse will be measured as an estimate of the heart rate after the patient has rested for 5 minutes.
- Blood pressure: 3 measurements separated by 5 minutes each will be taken, for which the patient should be at rest and sitting. The first measurement will be discarded and the values obtained at the second and third measurements will be averaged, a mean value that will be recorded in the medical history and in the case report form (CRF).
- Electrocardiogram
- The patient will be scheduled for visit 2, which corresponds to randomization.

12.3.2 Randomization visit 2 (week 0)

Visits will be scheduled a week after the baseline screening visit with a window of ± 3 days from the respective date.
The following tasks will be carried out in the consultation during this visit:

- Review the inclusion and exclusion criteria.
- Pulse, will be measured after the patient has rested during 5 minutes.
- Blood pressure: 3 measurements separated by 5 minutes each will be taken, for which the patient should be at rest and sitting. The first measurement will be discarded and the values obtained at the second and third measurements will be averaged, a mean value that will be recorded in the medical history and in the case report form (CRF).
- Patient will be randomized. A randomization number and treatment with HEMAX PFS or EPREX/ ERYPO® will be assigned to each eligible patient.
- Study medication will be dispensed. Patients will receive the study medication (including oral iron supplement) free of charge; in addition, patients will be instructed on the administration of the medication and will be given a card to register dose administration.
- Subcutaneous administration of HEMAX PFS or EPREX/ ERYPO® will be performed.
- The prescribed doses of HEMAX PFS or EPREX/ ERYPO® will be recorded.

- The patient will be scheduled for the next visit, that corresponds to study week 2.

12.3.3 Visit 3, 4, 5, 6, and 7 (weeks 2, 4, 6, 8 and 10 respectively)

Visits will be scheduled two weeks after the prior visit with a window of ± 1 week from the respective date.
The following tasks will be carried out in the consultation in each of these visits:

- Blood pregnancy test (only in women of childbearing potential)
- Pulse, will be measured after the patient has rested for 5 minutes.
- Blood pressure: 3 measurements separated by 5 minutes each will be taken, for which the patient should be at rest and sitting. The first measurement will be discarded and the values obtained at the second and third measurements will be averaged, a mean value that will be recorded in the medical history and in the case report form (CRF).
- Complete hemogram. The result of the local hemoglobin test should be within the same day or before, so as to be able to adjust the study medication dose, if required.
- The study medication will be counted and dispensed, and patients will be given a card to record the application of the doses.
- Subcutaneous administration of HEMAX PFS or EPREX/ ERYPO® will be performed.
- The prescribed doses of HEMAX PFS or EPREX/ ERYPO® will be recorded, controlling the returned empty boxes and the dose recording cards.
- Adverse events will be recorded and will be registered in the medical history and in the CRF.
- The patient will be scheduled for the next study visit.

12.3.4 Visit 8 (week 12)

The following tasks will be carried out in the consultation during this visit:

- Review the criteria for entry in the maintenance phase.
- Blood pregnancy test (only in women of childbearing potential)
- Samples for full local laboratory test, consisting of:
  - Complete hemogram with reticulocyte and platelet count.
  - Hepatogram,

- Glycemia, lipid profile (HDL, LDL and triglycerides)
- Ionogram, calcium, phosphorus, urea and creatinine,
- Serum iron, transferrin, transferrin saturation, and ferritin
- Serum sample for antibodies and hepcidin dosage (the sample will be collected and stored for further analysis)

- Pulse, will be measured after the patient has been at rest during 5 minutes.
- Blood pressure: 3 measurements separated by 5 minutes each will be taken, for which the patient should be at rest and sitting. The first measurement will be discarded and the values obtained at the second and third measurements will be averaged, a mean value that will be recorded in the medical history and in the case report form (CRF).
- The study medication will be counted and dispensed, and patients will be given a card to record the application of the doses.
- Subcutaneous administration of HEMAX® PFS or EPREX/ ERYPO® will be performed.
- The prescribed doses of HEMAX® PFS or EPREX/ ERYPO® will be recorded, controlling the returned empty boxes and the dose recording cards.
- Adverse events will be recorded and entered in the medical history and in the CRF.
- The patient will be scheduled for the next study visit.

12.3.5 Visits 9 and 10 (weeks 16 and 20 respectively)

The visits will be scheduled four weeks after the previous visit with a window of ± 1 week from the respective date.
The following tasks will be carried out in consultation during these visits:

- Blood pregnancy test (only in women of childbearing potential)
- Pulse, will be measured after the patient has been at rest during 5 minutes.
- Blood pressure: 3 measurements separated by 5 minutes each will be taken, for which the patient should be at rest and sitting. The first measurement will be discarded and the values obtained at the second and third measurements will be averaged, a mean value that will be recorded in the medical history and in the case report form (CRF).
- Complete hemogram. The result of the local hemoglobin test must be within the same day or before so as to be able to adjust the study medication dose, if required.
- The study medication will be counted and dispensed, and patients will be given a card to record the application of the doses.
- Subcutaneous administration of HEMAX PFS or EPREX/ ERYPO® will be performed.

- The prescribed doses of HEMAX PFS or EPREX/ ERYPO® will be recorded, controlling the returned empty boxes and the dose recording cards.
- Adverse events will be recorded and entered in the medical history and in the CRF.
- The patient will be scheduled for the next study visit.

12.3.6 Visit 11 (week 24) or end - of - study visit

This visit will be scheduled four weeks after the previous visit with a window of ± 1 week from the respective date.
The following tasks will be carried out in the consultation during this visit:

- Blood pregnancy test (only in women of childbearing potential)
- Samples for full local laboratory test, consisting of:
  - Complete hemogram with reticulocyte and platelet count.
  - Hepatogram,
  - Glycemia, lipid profile (HDL, LDL and triglycerides)
  - Ionogram, calcium, phosphorus, urea and creatinine,
  - Serum iron, transferrin, transferrin saturation, and ferritin
  - Serum sample for antibodies and hepcidin dosage (the sample will be collected and stored for further analysis)
- Pulse, will be measured after the patient has been at rest during 5 minutes.
- Blood pressure: 3 measurements separated by 5 minutes each will be taken, for which the patient should be at rest and sitting. The first measurement will be discarded and the values obtained at the second and third measurements will be averaged, a mean value that will be recorded in the medical history and in the case report form (CRF).
- The prescribed doses of HEMAX PFS or EPREX/ ERYPO® will be recorded, controlling the returned empty boxes and the dose recording cards.
- Medication accounting will be performed
- Adverse events will be recorded and entered in the medical history and in the CRF.

12.3.7 Unscheduled visit

An unscheduled visit can be made at any time during the study, if the patient requests so or in the event that the investigator deems it necessary. The date and the reason for the unscheduled visit will be

recorded in the medical history. The following items will be recorded in the CRF:

- adverse events,
- changes in medication and concomitant medications.

All the other activities and evaluations are optional according to the investigator's judgment.

13 INVESTIGATIONAL PRODUCT/ STUDY DRUGS

13.1 METHOD OF PATIENT ALLOCATION TO A TREATMENT GROUP

All patients will be randomized by an electronic randomization system, stratified by sex and in blocks by site.

13.2 BLINDING

This is not applicable as this is an open-label study.

13.3 CODE UNBLINDING DUE TO EMERGENCY

This is not applicable as this is an open-label study.

13.4 POST STUDY ACCESS

If at the end of the study, the patient has the indication to continue with the treatment with epoetin and his current healthcare provider does not provide it, BIOSIDUS will provide the patient with epoetin (Hemax PFS® or Hemax®) free of charge until it becomes available through patient's healthcare provider.

13.5 INVESTIGATIONAL PRODUCT/ STUDY DRUGS DESCRIPTION

HEMAX PFS will be used in prefilled syringe in 1000 IU/ 0,5ml, 2000 IU/0,5ml, 3000 IU/0,3ml and 4000 UI/0,4ml presentations.
The sponsor Biosidus Argentina SA, is responsible for the manufacture of HEMAX PFS in accordance with the Good Manufacturing Practice (GMP) guidelines.
The solution for injection should be kept in the refrigerator, at a temperature between 2°C and 8°C.
EPREX/ ERYPO® injectable in prefilled syringe in 1000 IU/0,5ml, 2000 IU/0,5ml, 3000 IU/0,3ml and 4000 IU/0,4ml.presentations will be used as reference.
The manufacturer Janssen Cilag, Germany, is responsible for the manufacture of Eprex/ ERYPO® in accordance with the Good Manufacturing Practice (GMP) guidelines.
The solution for injection should be kept in the refrigerator, at a temperature between 2°C and 8°C. The study drugs will be dispensed according to the following diagram:

Medication	Presentation to be dispensed	Titration phase (week 0 to week 12)	Maintenance phase (week 12 to week 24)
HEMAX®	Injectable, 2000 IU/ 0.5ml and 4000 IU/ 0.4 ml in a sufficient amount depending on the dose to be administered.	The initial dose will be 29IU/ kg estimated for an average weight of 70 Kg, what equals to 2000IU twice a week.	The weekly dose will be estimated based on the total dose that the patient was receiving until week 12. That is to say, a patient that was receiving 2000IU/ 0.05 ml twice a week will start to receive 4000IU/ 0.4ml on a weekly basis
		Dose adjustments will be in aliquots of 25% of the dose that the patient was receiving	Dose adjustments will be in aliquots of 25% of the dose that the patient was receiving
		It is estimated that the mean weekly dose will be 5000 IU ± 2500 IU/ ml.	It is estimated that the mean weekly dose will be similar to the weekly dose administered twice a week.
		Given that visits are every 2 weeks and that in each visit the medication will be administered at the site, only the necessary amount for the biweekly dose (3 doses) will be dispensed which will not be administered at the site.	Given that visits are every 4 weeks and that in each visit the medication will be administered at the site, only the necessary amount for the weekly dose (3 doses) will be dispensed which will not be administered at the

site.

The drug supplies should be stored in a safe place, in a refrigerator with limited access and in appropriate conditions, with temperatures between 2º C and 8º C. Only authorized staff will have access to the study drug at study sites.
Patients will also be administered supplements of:

- **Ferrous sulphate**, tablets of 200 mg that will be presented in the packaging with the approved package insert for use in our country and which will be administered according to the criterion of the investigator in order to maintain the transferrin saturation above 20% during the study.

13.6 ACCOUNTABILITY AND COMPLIANCE

The patient will return all the study drugs both used and not used. The site staff will only record in the source document and in patient's individual accountability record the patient number and the number of study drug packages returned.
During the study, the monitor will continuously review all the study drugs (bottles used and unused) and the corresponding accountability forms. Also the card where the patient will record the administered medication doses will be reviewed at each visit. The accountability records of the study drugs will be filed at all times at the sites. At the end of the study, a final accountability will be performed and all the remaining drugs will be removed for destruction according to the current regulations.

14 EVALUATION METHODS

14.1 METHODS OF 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
- Percentage of responder patients, defined as the increase of Hb ≥1g/ dl without transfusion requirement.
- Number and percentage of patients that require at least one transfusion.

14.2 SAFETY PARAMETERS

14.2.1 Adverse events

Adverse events will be recorded from the moment in which the patient signs the informed consent and will be recorded throughout the study. These should be reviewed and updated at each subsequent visit and during any telephone contact with the patient.

14.2.2 Vital signs

Pulse and blood pressure measurements will be made at each visit.

14.2.3 Medical history

At baseline visit (week - 1), a medical history will be made and all clinically relevant data will be recorded in the source documents of the patient and in the individual case record form (ICRF). The medical history will include the registration of the concomitant medication which will be recorded in the source documents of the patient and in the individual case record form (ICRF), which will be updated as changes occur at each visit.

14.2.4 Physical exam

At baseline visit (week - 1), a physical examination will be performed and all clinically relevant data will be recorded in the source documents of the patient and in the individual case record form (ICRF).

14.2.5 Physical Examination

A brief physical examination will be performed at the baseline visit (week -1) and all clinically relevant data should be recorded in the patient's source documents and on the individual case record form (ICRF).

14.2.6 Electrocardiogram

At baseline visit (week - 1) an electrocardiogram will be performed and all clinically relevant data will be recorded in the source documents of the patient and in the individual case record form (ICRF).

14.2.7 Full laboratory tests

A full laboratory test will be performed at the baseline visit (week - 1) and at the
week 12 and week 24 visits or at study completion visit and all clinically relevant data will be recorded in the source documents of the patient and in the individual case record form (ICRF). Samples for full local laboratory test will consist of:

- Complete hemogram with reticulocyte (through flow cytometry or hematologic counter) and platelet count.
- Hepatogram,
- Glycemia, lipid profile (HDL, LDL and triglycerides)

- Ionogram, calcium, phosphorus, urea and creatinine,
- Serum iron, transferrin, transferrin saturation, and ferritin
- Beta subunit of chorionic gonadotropin only in women of childbearing potential
- Serum/ plasma sample for antibodies and hepcidin dosage (the sample will be collected and stored frozen at - 20º C for further analysis)

14.2.8 Complete hemogram

A complete hemogram will be performed at week 4, 6, 8, 10, 16 and 20 visits and all clinically relevant data will be recorded in the source documents of the patient and in the individual case record form (ICRF). The result of the local hemoglobin test must be within the same day or before so as to be able to adjust the study medication dose, if required.

14.2.9 Blood pregnancy test

A blood pregnancy test will be performed only in women of childbearing potential at week -1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 visits. All clinically relevant data will be recorded in the patient's source documents and in the individual case record form (ICRF).

15 SAFETY AND ADVERSE EVENTS

Adverse events

An adverse event (EA) is defined as any undesirable medical condition, in a patient in a clinical trial to whom a medical product was administered, without necessarily having to present any causal relationship with the treatment.

In the study, any event that occurs once the patient included in the clinical trial has signed the study informed consent and has received at least one dose of the study medication should be recorded and reported as an AE.

An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal product under investigation, whether or not considered related to that medical product.

For adverse events with a causal relationship to the investigational product, the investigator will be required to follow up until the event or its sequelae resolve or stabilize to a level acceptable to the investigator.

A new problem or the worsening of a preexisting one will be considered as an AE. A stable chronic problem, such as arthritis that exists before the start of the study and that does not worsen during the same will not be considered an AE.

An abnormal result from a diagnostic procedure, including abnormal laboratory findings, will be considered as an AE when:

- It results in the withdrawal of the patient by the investigator
- It is associated with a serious adverse event (SAE)

- It is associated with clinical signs or symptoms
- The physician considers it clinically relevant

The investigator will establish, according to his own criterion, if the AEs do or do not have a **causal relationship with the study drug,** in accordance with the following assessment of causality of adverse reactions possibly related to the study drug.

The following 4 - point scale will be used to establish the **causality relationship**:

- **Unrelated:** Events that do not follow a reasonable temporal sequence from the administration of the study drug or that can be reasonably explained by the base disease, complications, concomitant medication or treatment or environmental factors.
- **Possible**: Event that follows a reasonable temporal sequence from the administration of the study drug (including study medication suspension or dose reduction) with reasonable possibility that the adverse event has been caused by the study medication but also may have been caused by the base disease, complications, concomitant medication or treatment or environmental factors.
- **Probable**: Event that presents a clear temporal relationship, with improvement upon study medication suspension or dose reduction and when the causality due to other factors such as the base disease, complications, concomitant medication or treatment or environmental factors can be reasonably excluded.
- **Defined**: Event with clear temporal relationship, with improvement upon study medication suspension or dose reduction and recurrence upon treatment reinitiation.

Depending on its **intensity or degree of severity,** the AEs are classified as follows:

- **Mild:** It does not significantly interfere with the daily activities of the subject, disappears without leaving any residual effect.
- **Moderate:** It significantly interferes with the study and/ or with the daily activities of the subject, and may or may not require treatment.
- **Severe**: It significantly interferes with the study and/ or with the daily activities of the subject, it requires treatment or suspension of the study medication and is considered as unacceptable at the physician or the patient's criterion and may require withdrawal from the study.

A **serious adverse event (SAE)** is defined as an AE that results in any of the following results:

- Death;
- Life threat;
- Requires or prolongs hospitalization;

- Causes persistent or significant inability / disability;
- It is a congenital anomaly or birth defect;
- It is a major medical event that requires a medical intervention to prevent the results mentioned in the previous points.

Important medical events are those that may not be immediately life threatening but that may endanger the patient and require an intervention to prevent one of the other serious results listed above. Examples would be an intensive treatment in the emergency room or at home due to an allergic bronchospasm, blood dyscrasia or seizures that do not result in hospitalization but that, if not treated, would have threatened the life or resulted in death; an adverse event of this type, resolved, will be considered as serious according to this criterion.

The **hospital admission** or the prolongation of an existing hospitalization means that the patient's admission to the hospital for more than 24 hours and/ or the prolongation of the hospitalization was necessary for the treatment of an AE or that it occurred as a result of the event. It does not refer to a preplanned elective hospital admission for the treatment of a preexisting disorder that has not significantly worsened, nor to diagnostic procedures.
The term **"life - threatening"** in the definition of "serious" refers to an event in which the patient ran a risk of death at the time of the event; it does not refer to an event which hypothetically could have caused the death had it been more severe.
Any new SAE that occurs after the study period and is considered related (reasonable possibility) with the study drug or with the participation in the study, must be registered and reported immediately. The study period for SAE reporting is defined as the period from the time of the signing of an informed consent until the end of the follow - up period (30 days after the last dose).

SAE reporting: To comply with the regulatory requirements, any serious adverse event, considered related or not with the study drug, should be brought to the attention of the sponsor or designee as soon as the investigator or the coordinator becomes aware of the same. The SAE form must be completed and sent without delay, even if not all information was available at the time of the initial contact.
The SAE must be reported to the sponsor or designee within 24 hours after becoming aware of the event.
The SAEs occurred in Argentina will be sent directly or through the person responsible for monitoring the clinical study to:

Biosidus, Departamento de Investigación Clinica
Constitucion 4234
(1254) Buenos Aires

Phone: 54 - 11 - 4909 - 8049 / 8000

FAX 54 - 11 - 4924 - 3601

Any relevant additional follow - up information on a SAE that was not possible to provide in the initial report will be sent by the site within 24 hours from the moment on which the new information is obtained.
The *Unidad de Seguridad de Medicamentos* of Biosidus S.A. will make a pharmacovigilance report for those cases that require so, in order to notify to the appropriate authorities, in accordance with the current regulations.

Pregnancy reports: Pregnancy reports should be sent to the *Unidad de Seguridad de Medicamentos* of Biosidus S.A. so as to be included in the safety database. This also 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 ICRF, provided by the sponsor.
The procedure for pregnancy reporting must be the same as the procedure for SAE reporting.

16 STATISTICAL METHODOLOGY

16.1 SAMPLE SIZE JUSTIFICATION

A total N 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.

16.2 RANDOMIZATION

All patients will be randomized by an electronic randomization system, stratified by sex and in blocks by site.

16.3 PATIENT DATA ANALYSIS GROUPS

The data analysis groups or populations are listed below.

16.3.1 Full Analysis Set (FAS)

The full data analysis group will consist of all patients enrolled in this study that have been randomized and who have received at least one dose of the study medication.

16.3.2 Per Protocol (PP) analysis group

The per protocol data analysis group will consist of all patients enrolled in this study who have received at least one dose of the study medication, who have completed at least one follow - up visit and that do not have major protocol violations.

16.4 DATABASE ANALYSIS

There will be two formal database analyses.

- A first 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.

- A second 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.

16.5 EFFICACY ANALYSIS

The efficacy analysis will be performed for both FAS and PP populations. Descriptive statistics and inferential statistics will be performed through intergroup analysis (ANCOVA covariance analysis)- comparing each treatment group (patients treated with HEMAX PFS versus those treated with EPREX/ ERYPO®) and an additional intragroup analysis analyzing 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%. Statistical analysis will be performed with SPSS software or equivalent.

The following parameters will be evaluated for treatment efficacy, according to the objectives defined by the protocol.

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%.

The **secondary efficacy assessment** will be carried out through the evaluation of the following objectives:

- 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.

For **missing hemoglobin data**, the last observation carried forward method will be used.

In an exploratory way, the basal level of hepcidin at 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.

16.6 SAFETY ANALYSIS

The evaluation of safety shall be carried out using the entire population (FAS) of data, making focus on adverse events (AE).
As primary 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,
- A**ntibody 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 and x2 test will be performed to compare the incidence of adverse events and adverse reactions of patients treated with HEMAX® PFS versus those treated with EPREX/ERYPO®.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 COMPLIANCE WITH THE REGULATIONS APPLICABLE TO CLINICAL TRIALS

The study will be carried out in accordance with the laws, regulations and administrative requirements related to the implementation of Good Clinical Practice in the conduct of clinical trials with medications for human use, as determined by the current national/ local regulations, applicable ANMAT dispositions, the current version of the Declaration of Helsinki and the ICH guidelines.

17.2 INFORMED CONSENT

The principles of informed consent will be followed, in accordance with the national/ local current regulations, the current version of the Declaration of Helsinki and the ICH guidelines. A patient should not enter into the clinical trial or perform any study - related procedure until he/ she has been duly informed, has been given time to consider his/ her participation and has given his/ her consent freely by signing and dating the informed consent approved by the Institutional Ethics Committee of Clinical Research (IECR). This must occur before any study - related procedure is performed.
The proposed consent form and any of the other documents relevant to the consent process, must be submitted to the IECR together with the protocol and must be approved prior to study initiation.
A signed and dated copy of the informed consent form and any other document in relation to the consent process will be given to the patient; the original document will be kept at the site.
The Informed Consent details some aspects of special interest that are listed below:

> POTENTIAL EXPECTED BENEFITS.
> You may not get any benefit from participating in this study, the potential benefits are in the future for patients with the same disease. However, it is expected that you will obtain the same effect with HEMAX PFS® as the one described with the previous formulation HEMAX® and EPREX/ERYPO®, which is the increase in red blood cell levels in patients with chronic kidney disease and anemia.
>
> COSTS

For the patient
This study is being funded by Biosidus S.A. who has established a contract with your doctor/center for all costs and professional fees associated with your participation in this study. Your participation in this study will not result in any costs to you or your medical coverage. Biosidus S.A. will provide you with study medication (including oral iron supplements if indicated) at no charge. Medical visits, physical examinations, procedures, treatments (including contraceptive methods required by the study) or tests that are not included in your usual medical care, and that are required only for the purposes of this study, will be provided at no charge to you or your health care system. In addition, if after the study, you have indication to continue with epoetin treatment and your current health system does not provide it, Biosidus S.A. will provide you with epoetin (Hemax PFS® if approved by ANMAT or Hemax® which is the formulation currently marketed) free of charge until it is available through your health system.

Payment for participation in the study
You will not receive any payment for your participation in this study. However, you will be reimbursed for travel expenses related to study visits upon signature of the acknowledgement of receipt and/or presentation of the original receipts for expenses incurred for this study.

COVERAGE IN CASE OF DAMAGE WHAT HAPPENS IF YOU SUFFER AN ADVERSE EVENT AND/OR REACTION OR DAMAGE TO YOUR HEALTH?
If during the study you suffer an adverse event or a consequence to your health related to the medication or procedures of the study, Biosidus S.A. will provide you with all the immediate and necessary medical assistance for your treatment. The costs of such assistance will be borne by the sponsor. Likewise, Biosidus S.A. will be responsible for any damage to your health resulting from your participation in the study. Biosidus S.A. has taken out an insurance policy (policy #44927) with the firm CHUBB ARGENTINA DE SEGUROS S.A. with address at Hipólito Bouchard 710, 11th and 12th floors, Ciudad Autónoma de Buenos Aires, telephone 54-11-4510-1500, in case of any damage to your person. By signing the informed consent form, you do not waive your rights under the Civil and Commercial Code and Argentine laws regarding civil liability for damages.
If you agree, your primary care physician will be informed about your participation in this study.

17.3 INSTITUTIONAL ETHICS COMMITTEE FOR RESEARCH (IECR) / INSTITUTIONAL REVIEW BOARD (IRB)

The study must have written approval from the IECR. Before the beginning of the study, the sponsor or its designee must receive a copy of the letter of approval from the IECR, which will contain the specific identification of the approved documents.
Any relevant amendments to the protocol or subsequent changes in the informed consent form as a

result of the changes in the protocol and/ or Investigator's Brochure approved by the sponsor must also be approved by the IECR and the documentation of this approval will be provided to the sponsor. The records of the IECR review and the approval of all the documents relevant to this study will be kept in the file of the investigator and will be subject to an audit by the sponsor and/ or the regulatory authority during or after study completion. All study documents should be kept for a period of ten years or more according to the current regulations.
In addition, the investigator or sponsor will communicate to the IECR any serious adverse event (SAE) or other according to its regulations.
As needed, periodic reports of the trial progress as well as the notification of study end and a final report, where applicable, will be submitted to the IECR. A copy of all reports submitted to the IECR will also be sent to the sponsor.

17.4 PROTOCOL AMENDMENTS

Protocol changes should only be performed by an approved amendment to the protocol. Protocol amendments must be approved by the sponsor, the IECR of reference and the IECR of each site (if applicable), prior to their implementation.

17.5 CLINICAL STUDY COMPLETION STATEMENT

For all the sites participating in the trial, there will be an end of clinical trial notification to the IECR.

17.6 PATIENT CONFIDENTIALITY

All patient data are identified only by a patient identification number and the existing laws on personal data protection will be respected.
After obtaining the consent from the patient, the investigator will enable the study monitor, the independent auditor or the regulatory agency staff to review the part of the medical history of the patient that is directly related to the study. This will cover all relevant study documentation, including the medical history of the patient, to verify eligibility, summaries of hospitalization/ discharge from any hospitalization that could occur during patient's participation in the study and the reports of autopsies of deaths occurring during the study (if applicable).

17.7 RESPONSIBILITY AND SAFETY

Biosidus Argentina SA will provide a Certificate of Insurance Policy of Clinical Trial to the study sites with the corresponding coverage according to the local current regulations.

18 DOCUMENTATION

18.1 STUDY ARCHIVE AND SITE DOCUMENTATION

Before the start of the study, the following documents must be received by the sponsor from the site:

1) Confidentiality Agreement.
2) Signed protocol pages, amendments and notifications.
3) Curriculum Vitae of the principal investigator and medical license.
4) Investigator's statement.
5) Clinical Trial Agreement signed.
6) Written approval of the IECR for the protocol, amendment(s), informed consent form, patient information sheet (if applicable) and advertising (if applicable).
7) List of the IECR members. Committee SOPs.
8) Other forms that are applicable according to the local current regulations.

18.2 STUDY DOCUMENTATION PROVIDED BY THE SPONSOR

The sponsor will provide the investigator with the following documents:

- Protocol final version.
- Informed consent (final version).
- Current version of HEMAX PFS package insert project and EPREX/ ERYPO® package insert, which will constitute the product information.
- A printed copy of the ICRF.
- Regulatory document files.
- Certificate of insurance and/ or insurance policy.

18.3 DATA MAINTENANCE AND RETENTION

It is the responsibility of the site investigator to maintain, in an exhaustive and centralized manner, a system for collecting all the relevant information.
Investigators will be informed that they should keep all study records in a safe place and with limited access during a period of ten years or more according to the applicable current regulations.

Investigators will be informed that before eliminating any study data/ document, they have to consult it with the Sponsor, as well as to notify in writing any change in location, availability or custody of the study files.

18.4 DATA MANAGEMENT

18.4.1 Data capture through Individual Clinical Record Form (ICRF)

18.4.1.1 Data capture

The sponsor will provide each study site with a printed copy of the reference template for data capture (ICRF) in carbonless paper or digital form, sending a copy to the site and another to the sponsor.
Data entry at the site will be made by the investigator, study coordinator or other study staff properly trained and designated.
The ICRFs are used to keep the study data and are an integral part of the study and subsequent reports. Therefore, the ICRFs must be completed for each patient recruited in accordance with the source data of the patient at every visit.
Patients should not be identified by the name. An appropriate coded identification will be used so that they cannot be identified (if applicable). The site investigator should maintain a separate form with the names of the patients, the non - identifying initials (if applicable) and the addresses of the patients (a patient identification form).
Each completed ICRF must be verified by the site investigator at each visit and should be contrasted with the source documents of the patient by the clinical trial monitor. Each entry must be monitored by the monitor and by the staff from the *Procesamiento de Datos* department (DM).

18.4.1.2 Discrepancy Management

The internal consistency and the integrity of the data entered in the study database are defined by a series of validations. A deviation from these predefined and automated validations, may create an inconsistency in the database that can be resolved by using a data correction form.
There are 2 main types of discrepancies:

- Automatic discrepancies automatically generated during data entry or following data logical execution.
- Manual discrepancies, that can be generated by a system user at any time.

It will be the responsibility of the investigator and his team to resolve any data discrepancy in due time and manner. The study monitors will perform the follow - up to confirm that these discrepancies are resolved.

18.5 ADDITIONAL DOCUMENTS AND RECORDS

1) Patient selection and allocation form: A list of all patients who have signed the informed consent and that have been selected.
2) Patient identification form: Allows the investigator to associate the selected patient with the study. This information will include, but will not be limited to only: patient name, date of birth, contact information and non - identifying patient initials (if applicable). This confidential list must be kept at the research site and will not be sent to the sponsor.
3) Drug accountability form: This form reflects the total amount of study drug that has been dispensed and returned by each patient in the relevant study visits.

19 QUALITY ASSURANCE AUDITS

19.1 QUALITY ASSURANCE PROGRAM

This clinical trial can be audited in accordance with the Quality Assurance (QA) Program of the sponsor.
The purpose of these audits is to determine if this study is being conducted or monitored in accordance with both the Protocol, and with the GCP guidelines and local regulations. These audits will also increase the credibility of the study data, so that any type of study documentation may be required by any regulatory authority for inspection. These audits, if performed, will be scheduled with the site and will be carried out in a reasonable period of time.

19.2 REGULATORY INSPECTIONS AND AUDITS

The study may be inspected by regulatory agencies and audited by ethics committees. These inspections/ audits will take place at any time during or after the study and will be performed in accordance with the national regulations as well as the ICH guidelines.

20 STUDY MONITORING

20.1 MONITORS AND MONITORING VISITS

The study monitor will be responsible for ensuring compliance with the current Good Clinical Practice guidelines, the ICH guidelines and the standard operating procedures of the sponsor or designee. The study monitors will be designated by the sponsor. The monitors will observe the current Good Clinical Practice guidelines, the ICH guidelines and the standard operating procedures of the sponsor or designee.

Regular monitoring of the study data in accordance with the specific study monitoring plan will be conducted. Individual sites will be monitored to check the pace of recruitment, data and protocol compliance. The frequency of monitoring of individual sites may depend on the pace of recruitment, the quantity of data collected and the complexity of the study, variables that will be documented in the monitoring plan.
These monitoring visits will be carried out with the purpose of verifying the protocol compliance as well as the accuracy of the data and that these are collected in the ICRF. The study monitor will verify the entries in the ICRF comparing them with the main source of information (hospital/ clinic/ official records), which must be available for this purpose. The monitor will review the maintenance of official documentation and the study medication accountability. The monitor will periodically review study progress along with the site investigator and the other people participating in the study. At study end, there will be a monitoring closure visit. Monitoring visits will be scheduled in advance with the site staff by mutual agreement and at an acceptable time for both. The site staff should provide sufficient time to the monitor for the review of the ICRFs as well as of the source documents. The coordinator and/ or investigator will answer any question or provide any clarification in relation to the data. The site investigator must provide a place and a time suitable for those visits to be performed.

20.2 MAIN SOURCE DOCUMENTS

The investigator should retain the primary documentation sources for data entry in the ICRF. These documents, considered as "source documents", should include, but will not be limited to:

- Anthropometric and demographic information.
- Evidence that supports the diagnosis/ condition for which the patient is being studied.
- General information to support patient participation in the study.
- Medical information and physical examination findings.
- Records of hospitalizations or emergency visits (if applicable).
- Each study visit must be dated including any relevant finding/ note found by the investigator; occurrence (or absence) of adverse events, as well as changes in the use of the medication, including the start and end date of drug administration.
- Any additional visit during the study.
- Any relevant telephone conversation with the patient related to the study or to a possible adverse event.
- The original informed consent form signed for study participation.

The investigator must also keep all those printed documents/ test/ procedure reports performed that are requested in this study. During the monitoring visits, the monitor will need to verify the ICRF data, comparing them with the source information.

21 USE OF INFORMATION AND DATA PUBLICATION

All information provided by the sponsor in connection with this study, which has not been previously

published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure (if applicable), clinical protocol, data capture notebooks and other scientific data. Any data collected during the study are also considered confidential. This confidential information will remain the exclusive property of the sponsor, it will not be disclosed to third parties without the written consent of the sponsor, and it will not be used for other purposes than study conduct.
The information developed during the conduct of this clinical study is also considered confidential and will be used by the sponsor in connection with the development of the drug. The information must be disclosed as considered by the sponsor. To allow the use of information derived from this clinical trial, the investigator is obliged to provide the sponsor with the complete results and all data developed in this study. The information obtained during this study may be available for other investigators who are conducting similar studies.
If the investigator wishes to publish the data from this study, he must deliver a manuscript to the sponsor for review 60 (sixty) days before its publication. In the event that the sponsor chooses to publish this study data, it will deliver a copy to the investigator at least 30 days before the presumed date of delivery to the defined editor. Any publication resulting from this research should include the investigators who participated on behalf of the sites and Biosidus, according to the usual criteria of authorship of scientific publications set forth in the Uniform Requirements for Manuscripts submitted to biomedical journals: Writing and editing for biomedical publication, from the International Committee of Medical Journal Editors.
The sponsor maintains the right to eliminate the confidential information from the manuscript and may make any objection to or suggestion regarding its publication and/ or the time of the publication (at the sponsor's full discretion).

22 SITE STAFF

22.1 RESEARCH SITE

The staff from each research site will consist at least of a Principal Investigator and a clinical study coordinator or sub-investigator.

22.2 PRINCIPAL INVESTIGATOR

At each research site, a physician will be designated to act as Principal Investigator and will bear overall responsibility for the management of the team of the site where the study will be conducted and for the study aspects at the appropriate site. The Principal Investigator will supervise the recruitment of patients, the correct conduct of the trial in accordance with the protocol and the requested data capture.

22.3 STUDY COORDINATOR OR SUBINVESTIGATOR

The study coordinator or sub-investigator will be appointed by the Principal Investigator and will be responsible for assisting the principal investigator in all those tasks that have been delegated to him.

23 SPONSOR

23.1 BIOSTATISTICS, DATABASE AND PROGRAMMING

The departments of Biostatistics, Database and Programming are responsible for the proper use of the data management application, of the completion of the common data management procedures and statistical analysis, as detailed in this Protocol. All procedures will be carried out in accordance with the local and ICH guidelines.
Based on the sponsor criterion, the biostatistics, database and programming tasks can be performed by a CRO.

23.2 CLINICAL MANAGEMENT

The local *Gerenciamiento Clinico* department (project leader or manager) is responsible for the daily activities of the local study and for ensuring that the sites and the Sponsor comply with all applicable regulations related to the clinical research.
Based on the sponsor criterion, this task can be performed by a CRO.

23.3 MONITOR

The monitor is responsible for monitoring the study in the participating sites. Monitoring visits will be agreed in advance and by mutual agreement at a time acceptable to both the monitor and the site staff.
Based on the sponsor criterion, this task can be performed by a CRO.

23.4 MEDICAL MONITOR

The Medical Monitor will be responsible for the periodic review of the clinical safety data and for the resolution of study - related medical issues.

25 INVESTIGATOR'S AGREEMENT

BIOSIDUS ARGENTINA SA

Protocol Nº BIOS - HPFS - 0115

I have carefully read beforehand the protocol, including all appendices and I agree that it contains all the information necessary for this study to be conducted safely.

I agree to conduct this study as indicated in the Protocol and in accordance with the Declaration of Helsinki (including its updates) and the current Good Clinical Practice Guidelines in force and applicable in each territory where the Clinical Study will be conducted, and I will try to complete the study within the defined deadline.

I agree to provide copies of the Protocol and any other information related to the preclinical and clinical trial experience to all team members that participate in the study. I agree to discuss with them this information and ensure that they are adequately informed in relation to the medication and the development of study.

I agree to keep all data and patient information (data capture notebooks, forms and medication dispensing and return forms and all the information generated during this study) by complying with the current Good Clinical Practice guidelines and local regulations.

Signature of the Principal Investigator: _____

Name of the Principal Investigator: _____

Date: _____

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