PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

A Multicenter, Double-Blind, Randomized, Comparative, Parallel-Group Clinical Study of the Efficacy and Safety of BCD-066 (JSC BIOCAD, Russia) and Aranesp® (Amgen Europe B.V., the Netherlands) in the Treatment of Anemia in Hemodialysis Patients with Impaired Kidney Function

Study Sponsor: JSC BIOCAD

Full name of Investigator:

____________________________________________________

Patient screening number / __ / __ / __ / __ / __ / __

Individual Patient Identification Code

(For Insurance Company)

Dear Participant,

Please take time to read the following information carefully. If you have any questions about your participation in the research study after reading it, please feel free to ask your study doctor. Please keep this document in case you need to refer to it at a later time.

Thank you for your interest in participating in this research study. The document you are reading will give you information about the research you are invited to take part in. You will be part of this research only if you decide to do that and the doctor agrees that you can participate. Please ask the study doctor or the study center staff if there is anything that is not clear or if you would like more information. Do not sign the Informed Consent Form if you do not want to or until you get all the answers you want and decide whether or not you wish to take part in this research.

You are being invited to take part in a multicenter, double-blind, randomized, comparative, parallel-group clinical study of the efficacy and safety of BCD-066 (JSC BIOCAD, Russia) and Aranesp® (Amgen Europe B.V., the Netherlands) in the treatment of anemia in hemodialysis patients with impaired kidney function.
STUDY RELEVANCE

Chronic kidney disease (CKD) describes the gradual, permanent loss of kidney function. Causes of CKD include birth defects that affect the kidneys, high blood pressure, diabetes, glomerulonephritis, and others. Kidneys do not only filter waste products from your blood but also produce the hormone called erythropoietin (EPO). This hormone stimulates production of red blood cells (RBCs). Red blood cells contain hemoglobin. Their main function is to deliver oxygen to the body tissues. Our body cannot live without oxygen. Damaged kidneys (for example, in people with CKD) cannot produce enough EPO. As a result, these patients have lower hemoglobin levels and RBC counts, which means they have anemia. All patients with CKD develop anemia.

Scientific findings show that anemia further complicates CKD. Patients with anemia have a higher risk of death (the lower the hemoglobin level, the higher the risk) and heart problems (such as enlargement of muscles in the heart, heart attack, or stroke). Anemia affects patients’ quality of life. Because their bodies do not receive enough oxygen, patients feel weak or tired, their ability to exercise becomes limited, and they may have problems with concentration or mood (for example, depression).

In the late stages of CKD, kidneys produce very little EPO. That is why the most effective way to treat CKD-related anemia is injections of exogenous (which means produced outside the human body) EPO. Nowadays, people do not need constant blood transfusions because they can receive injections of recombinant EPO, more than 90% of whose structure is similar to that of common human EPO. Using genetic engineering, scientists place the human EPO gene into animal cells. After that, the modified animal cells start producing EPO. Unfortunately, recombinant EPO has a short half-life. Because of that, patients need frequent injections. CKD requires life-long treatment, and repeated injections may considerably affect patients’ quality of life. New-generation EPOs, such as darbepoetin alfa, are produced using the same technology. Darbepoetin alfa is almost similar to natural human EPO, except that it has two additional sugar chains, thanks to which the drug remains thrice as long in the body as previous recombinant EPOs do. This change in the molecule’s structure helped reduce the frequency of injections to one in a week. Numerous controlled research studies conducted abroad have shown that darbepoetin alfa is very effective in the treatment of CKD-related anemia, similar to recombinant EPOs. Moreover, darbepoetin alfa remains in patients’ bodies for a longer time, so it can be injected less frequently. Only one drug containing darbepoetin alfa is approved for use in Russia. It is Aranesp® produced by Amgen Europe B.V. (the Netherlands).
Russian company JSC BIOCAD has developed its own drug containing darbepoetin alfa (code name: BCD-066). Physicochemical and animal studies showed that darbepoetin alfa produced by JSC BIOCAD stimulated the bone marrow. Because of this stimulation, the number of RBCs and the level of hemoglobin rose. Darbepoetin alfa was not toxic. These results have proved that darbepoetin alfa is low-toxic and can be recommended for human research.

We have already tested BCD-066 in humans. It was injected to healthy volunteers. The volunteers received one intravenous or subcutaneous injection. We tested BCD-066 to find out whether it stimulates the production of RBCs and reticulocytes (immature RBCs), which are the cells preventing us from anemia. In our research, a single injection of BCD-066 considerably increased the number of reticulocytes; their level peaked a week after the injection. There were no differences in reticulocyte levels between volunteers who had received BCD-066 and those who had received Aranesp®, which is the original darbepoetin alfa. BCD-066 is a biosimilar (biological copy) of Aranesp®. Both drugs had similar pharmacokinetics. This means they moved through and eliminated from the body in the same way. You should know that no unexpected unwanted effects occurred in volunteers who received BCD-066; all volunteers felt well and did not have complaints. Similar unwanted effects developed after injections of BCD-066 and Aranesp®. This information proves that if you decide to take part in this research study, you will receive effective and safe treatment, whether you receive one drug or another.

We invite you to take part in a research study that aims at finding out whether BCD-066 manufactured by JSC BIOCAD and Aranesp® produce equivalent (similar) effects in patients on hemodialysis who have CKD-related anemia.

You are already receiving treatment for anemia (epoetin alfa, epoetin beta, or darbepoetin alfa) once, twice, or thrice a week, and your treatment is effective. Darbepoetin alfa is as effective as epoetin alfa or epoetin beta, and it can be injected only once a week (sometimes even less frequently).

You should know that if you do not agree to take part in this research study, you can continue treatment with epoetin alfa, epoetin beta, darbepoetin alfa, or any other drug against anemia. If you do not want to take part in this research study, you may ask your doctor to recommend you any of these treatments. You do not have to take part in this research to receive treatment for your disease.
INFORMATION ON THE DRUG THAT IS BEING TESTED

Both drug products that are being tested, BCD-066 and Aranesp®, contain darbepoetin alfa as an active ingredient. Aranesp® (Amgen) has proved its high efficacy in numerous large research studies. It is widely used in clinical practice. Darbepoetin alfa is used to treat anemic patients with chronic kidney disease or cancer patients who developed anemia after having received chemotherapy.

Darbepoetin alfa is a biologically active protein, which is similar to human erythropoietin. Erythropoietin is mainly produced by the kidneys and to a lesser extent by the liver. Darbepoetin alfa is produced using a special cell technology. We DO NOT use blood collected from donors in the manufacturing of the drug.

BCD-066 has been developed by JSC BIOCAD (Russia). It is a biosimilar (copy) of original darbepoetin alfa, Aranesp®: it contains the same amount of active ingredient and has the same dosage form.

We have compared BCD-066 with Aranesp®. Tests showed that the drugs had the similar structure and physicochemical characteristics. We have finished several non-clinical research studies that compared pharmacology and toxicology of BCD-066 and Aranesp®. In these research studies, BCD-066 and Aranesp® produced similar effects. We have also completed a comparative double-blind randomized study of the pharmacokinetics/pharmacodynamics and safety of BCD-066 in comparison with Aranesp® in 74 healthy volunteers. In this study, BCD-066 and Aranesp® showed similar characteristics. Because the first clinical study with BCD-066 in healthy volunteers showed good results, we started a research on its efficacy and safety in patients on hemodialysis who have CKD-related anemia.

In this research, darbepoetin alfa will be injected at the end of a hemodialysis session, subcutaneously, once a week for 52 weeks. This means each injection of darbepoetin alfa falls on a day of the regular hemodialysis session. Your treating doctor will calculate your dose of darbepoetin alfa individually using a special equation. The dose of darbepoetin alfa will depend on the dose of epoetin alfa or epoetin beta that you have received within three months before you have started participating in this research. If you have received darbepoetin alfa before the research, you will continue using the same dose you have used within three months before you have started participating in this research. Your doctor will observe how you tolerate the treatment and how the hemoglobin level changes in your blood, and he/she may later change your dose of darbepoetin alfa.
You should know that long stimulation of the blood cell formation requires enough iron to supply its needs. That is why if you agree to take part in this research, you will also be given Venofer®. Your treating doctor will choose the dose of Venofer® for you individually. It will depend on the parameters of iron metabolism in your body.

PURPOSE AND OBJECTIVES OF THE RESEARCH STUDY

This research study has only scientific (experimental) nature (section 4.8.10 of Russian National Standard GOST R 52379-2005).

The reason we are doing this research is to study the efficacy and safety of BCD-066 (JSC BIOCAD) and Aranesp® (Amgen Europe B.V., the Netherlands) in patients on hemodialysis who have CKD-related anemia.

WHO ORGANIZES THE STUDY? WHAT INSTITUTIONS ARE INVOLVED?

This study is initiated and sponsored by JSC BIOCAD, a Russian biotechnology company. The company was founded in 2001; it is involved in research, development and manufacturing of drugs. BIOCAD develops drugs in its own research and development department and produces them in a modern plant in strict accordance with the international requirements.

The research study will take place in health centers accredited for conducting clinical studies as prescribed by the law.

DO YOU HAVE TO TAKE PART? WHAT CRITERIA SHOULD YOU MEET TO BE IN THE STUDY?

Your participation in this research is entirely voluntary. You do not have to participate in this study to receive treatment for your disease. You can take part in this research if:

• You have signed the Informed Consent Form.
• You are 18 to 75 years old (inclusive).
• You have end-stage kidney disease.
• You have needed hemodialysis for at least three months before you have started participating in this research study.
• You need in-hospital hemodialysis for at least 12 hours per week.
• Within the last three months, you regularly received epoetin alfa, epoetin beta, or darbepoetin alfa at the same dose and with the same frequency (once, twice, or thrice a week).
• Within three months before you have started participating in this research study, your hemoglobin level was ≥100 g/L and <120 g/L.
• Hemodialysis has been effective for you: dialysis dose (Kt/v) ≥1.2.
• Your transferrin saturation is ≥20%, your blood ferritin level is >100 ng/mL.
• You and your partner agree to use effective birth control methods during the research, from the screening and up to four weeks after you have received the last dose of the drug in the research study. This is required only if you can have children. Your birth control method is effective if you use a barrier contraceptive while your partner is using spermicide or oral contraceptive pills.
• You study doctor believes that you can follow the protocol procedures.

You cannot take part in this research if any of the following is true:
1. Your anemia is not related to kidney disease. For example, your anemia is caused by vitamin B₁₂ or folate deficiency, chronic blood loss, aluminum poisoning, or a chronic disease (C-reactive protein in your blood is >20 mg/L); or you have refractory anemia (that is unresponsive to treatment), and immature cells, called blasts, have been found in your blood.
2. You have lupus nephritis, or your kidney disease is caused by systemic vasculitis.
3. Your platelets are <100×10⁹/L.
4. Your hemoglobin is <100 g/L or >120 g/L.
5. You have scheduled kidney transplantation within the period of this research study.
6. Neutralizing or binding antibodies to erythropoietin were found in your blood.
7. You have experienced severe allergic reactions in the past (for example, anaphylactic shock), or you are allergic to multiple drugs.
8. You received a vaccination within 8 weeks before you have started participating in this research study.
9. You have cirrhosis of the liver, and you have developed such complications as portal hypertension (this is high blood pressure in the hepatic portal system), and/or splenomegaly (this is an enlargement of the spleen), and/or ascites (this is the accumulation of fluid in the abdomen).
10. You have tested positive for HIV, and/or active HBV, and/or HCV infection.
11. Your liver enzymes (AST, ALT) are more than three times higher than the upper limit of normal.
12. You have documented myelofibrosis (this is extensive scarring in your bone marrow).
13. You have a decompensated (which means severe, long-existing) heart disease such as severe heart failure (NYHA Class IV) or unstable angina (which means chest pain occurs frequently despite treatment).
14. You have severe uncontrolled arterial hypertension (high blood pressure). This means that either 1) your blood pressure remains high despite treatment with a combination of three antihypertensive drugs (those are drugs that decrease your blood pressure) after you have achieved your dry weight (your normal weight without any extra fluid in your body), or 2) your systolic blood pressure measured twice with a 15- to 30-minute interval, while you are lying on your back, is >180 mm Hg, or your diastolic blood pressure measured the same way is >105 mm Hg.
15. You have unstable angina (which means chest pain occurs frequently despite treatment).
16. You have an abnormal form of hemoglobin (hemoglobinopathy), a myelodysplastic syndrome, blood or lymphatic cancer.
17. You have pure red cell aplasia, which is a condition in which the bone marrow stops making red blood cells, causing severe anemia.
18. You have severe secondary hyperparathyroidism. This means that your CKD has caused more than a nine-time increase in the level of parathyroid hormone (produced by your parathyroid glands) compared to the upper limit of normal established in the laboratory where you have been tested.
19. You have experienced gastrointestinal bleeding within less than three months before you have started participating in this research.
20. Within less than six months before you have started participating in this research, you have had thrombosis (for example, a heart attack, a stroke, a transient ischemic attack, deep vein thrombosis, or pulmonary embolism).
21. You have had acute hemolysis, which is the excessive destruction of red blood cells.
22. You have had seizures and/or you have been diagnosed with epilepsy.
23. You had major surgery within one month before you have started participating in this research.
24. You received a blood transfusion within 3 months before you have started participating in this research study.
25. You have an acute or active chronic infection/inflammation, for example, a septic lesion (a boil or an abscess) or aseptic inflammation (hematomas, except for minor bruising around your vein that is punctured for hemodialysis).

26. You have a mental disorder that may place you at risk if you take part in this research. You have limited capacity.

27. You had or have cancer, except it is cured basal-cell carcinoma (a type of skin cancer) and/or cervical cancer in situ.

28. You abuse alcohol or drugs.

29. You are allergic or intolerant to any component of BCD-066 (JSC BIOCAD), Aranesp® (Amgen Europe B.V., the Netherlands), or other drugs of the same therapeutic class.

30. You are allergic or intolerant to any component of Venofer® (Vifor International Inc., Switzerland) or other drugs of the same therapeutic class.

31. You participated in another research within less than 30 days before you have started participating in this research, or you have already participated in this research study.

32. You are pregnant or breastfeeding a baby.

Your study doctor will carefully examine you before you start participating in this research. Your study doctor may refuse to approve your participation in the study if he/she decides that results of your tests do not allow you to get the study therapy.

You may change your mind later and stop participating even if you agreed earlier. This will not affect the quality of medical care you are getting at the moment or will get at any time in the future.

During the research period, we will give you all the new information that may affect your safety, or make you change your mind about being in the study.

If you decide to stop participating in the research for any reason, please inform your doctor about your decision as soon as possible.

You cannot take part in several studies at the same time.

You will be offered to sign an official Informed Consent Form when you have read it and asked all questions you may have.

**HOW WILL THE STUDY BE DONE? WHAT MEDICAL AND DIAGNOSTICS PROCEDURES WILL BE PERFORMED IN THE STUDY?**

This research is a double-blind study. This means that neither you nor your doctor will
know which drug you will receive. This is a randomized study. This means that the groups are selected by chance, as if by tossing a coin. This is also a parallel-group study. This means that you will receive only one of the study drugs: either BCD-066 or Aranesp®. This research study is also multicenter and comparative.

The research you are invited to take part in will include 196 patients on hemodialysis who have CKD-related anemia. All patients will be randomly divided (randomized) in two equal groups of 98 patients. You may receive one of the following treatment regimens:

- If you are in group 1, you will receive BCD-066 (JSC BIOCAD). It will be injected at the end of a hemodialysis session, subcutaneously, once a week for 52 weeks. Your treatment will be blinded. This means you will not know which of the drugs you are receiving.
- If you are in group 2, you will receive Aranesp®. It will be injected at the end of a hemodialysis session, subcutaneously, once a week for 52 weeks. Your treatment will be blinded. This means you will not know which of the drugs you are receiving.

The study will include the following periods:

1) The screening period:
   From day -28 to day 0 (before you have been randomized and started participating).

2) The main study period:
   During this period, you will receive the test drug or the reference drug. Your treatment will be blinded. Your study doctor will calculate your dose of the drug using a special equation. The dose will depend on the hemoglobin level in your blood. The study drug will be injected at the end of a hemodialysis session, subcutaneously, once a week. If your blood ferritin is <500 μg/L and transferrin saturation is <30%, this means that your body does not get enough iron for the chosen treatment regimen. If this happens, your doctor will give you Venofer®, an intravenous drug containing iron. This period will last for 24 weeks (about half a year).

3) The additional study period:
   The additional study period will last for another 28 weeks (about half a year). During this period, you will continue receiving the same drug.

   Drugs used in this research: the test drug, the reference drug, and Venofer® used for iron supply will be provided by the sponsor of this research study (JSC BIOCAD).

   On day 1, you will have to come to the study center in the morning, at least two hours before the scheduled time of the injection. All following visits to the study center (for hemodialysis and injections of the study drug) will be scheduled by your doctor.
All research procedures are necessary to monitor your health, control your disease, promptly detect any complications, and record any unwanted effect that may develop during this research.

**Study Visits and Procedures:**

This research will include the screening and 16 visits to the clinic: 2 assessment visits (days 169 and 365) and 14 routine visits.

Here you can find a short description of procedures performed at each visit:

- **The screening period** is performed not earlier than 28 days before you start participating in this research. During the screening examination, your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 24 mL of blood from your vein. This blood will be used for the following tests: complete blood count, blood chemistry tests, blood coagulation, intact parathyroid hormone, HIV, HBV, HCV infections, and antibodies to darbepoetin alfa. If you are a woman, we will also draw 3 mL of blood for a pregnancy test. We will also perform electrocardiography (ECG), echocardiography (ECHO), and chest X-ray. After that, your study doctor will assess your eligibility. This means that he/she will decide whether you can or cannot be in this research. If your study doctor decides that you can be in this research, he/she will schedule your next visit (day 1 visit). Your study doctor will randomly (which means by chance) put you into one of the research groups. This is called randomization.

- **Visit 1 (Day 1):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). At the end of the session, you will receive the first injection of the drug. The drug will be injected by a nurse of the study center (clinic). After that, your study doctor will ask you questions about your health, examine your body, measure your temperature, heart rate, and blood pressure. We will draw 3 mL of blood from your vein. This blood will be used for complete blood count test.

- **Visits 2, 3, 4 (Days 8, 15 and 22):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your study doctor will ask you questions about your health, examine your body, measure your temperature, heart rate, and blood pressure. We will draw 3 mL of blood from your vein. This blood will be used for complete blood count test.

- **Visit 5 (Day 29):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug.
Your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 8 mL of blood from your vein. This blood will be used for complete blood count and blood chemistry tests.

- **Visit 6 (Day 57):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your study doctor will ask you questions about your health, examine your body, measure your temperature, heart rate, and blood pressure. We will draw 10 mL of blood from your vein. This blood will be tested for complete blood count, parameters of your iron metabolism, and antibodies to darbepoetin alfa. We will perform electrocardiography.

- **Visit 7 (Day 85):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 8 mL of blood from your vein. This blood will be used for complete blood count and blood chemistry tests.

- **Visit 8 (Day 113):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your study doctor will ask you questions about your health, examine your body, measure your temperature, heart rate, and blood pressure. We will draw 10 mL of blood from your vein. This blood will be tested for complete blood count, parameters of your iron metabolism, and antibodies to darbepoetin alfa.

- **Visit 9 (Day 141):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your study doctor will ask you questions about your health, examine your body, measure your temperature, heart rate, and blood pressure. We will draw 3 mL of blood from your vein. This blood will be used for complete blood count test.

- **Visit 10 (Day 148):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your study doctor will ask you questions about your health, examine your body, measure your temperature, heart rate, and blood pressure. We will draw 8 mL of blood from your vein. This blood will be used for complete blood count and blood chemistry tests.
• **Visits 11, 12 (Days 155 and 162):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your study doctor will ask you questions about your health, examine your body, measure your temperature, heart rate, and blood pressure. We will draw 3 mL of blood from your vein. This blood will be used for complete blood count test.

• **Visit 13 (Day 169):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 20 mL of blood from your vein. This blood will be used for the following tests: complete blood count, blood chemistry tests, HIV, HBV, HCV infections, and antibodies to darbepoetin alfa. We will perform electrocardiography.

• **Visits 14 and 15 (Days 225 and 281):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 5 mL of blood from your vein. This blood will be tested for complete blood count and antibodies to darbepoetin alfa.

• **Visit 16 (Day 365):** You will undergo your regular hemodialysis session (the Sponsor of the research does not pay for this procedure). After that, you will receive the injection of the drug. Your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 20 mL of blood from your vein. This blood will be used for the following tests: complete blood count, blood chemistry tests, HIV, HBV, HCV infections, and antibodies to darbepoetin alfa. We will perform electrocardiography.

**You will finish participating in this research study on day 365.**

During the whole research period, your study doctor will ask you to tell him/her how you feel. It is necessary to monitor your health state and promptly notice any unwanted effect.

If you need to use a new drug during the study, you should ask your study doctor first. If you visit another doctor (except for the doctor performing the study), you should inform him/her that you are taking part in a clinical study and immediately inform your study doctor about it.
If you have any questions, feel free to ask your doctor. Please remember to inform your doctor about all changes in your health state.

SPECIAL NOTES TO STUDY PARTICIPANTS

Please inform your study doctor about all changes in your health. If you cannot come to the study center or continue participating in this research, please inform your study doctor as soon as possible.

YOUR RESPONSIBILITIES AS A STUDY PARTICIPANT

You will have to follow all rules and procedures required by your study doctor and the research protocol. You agree to inform your study doctor about all changes in your health whether they are related to the study drug or not.

You should know that we will have to withdraw (exclude) you from the research if you miss your scheduled visit and do not come to the study center within the following three days after it. If you have informed your study doctor that there is a force majeure event and you cannot come to a scheduled visit, or if a scheduled visit falls on a national holiday, you may come to the study center within the following seven days. If you have been excluded from the research study, we will perform the following visits:

- **Withdrawal Visit.** During this visit, your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 10 mL of blood from your vein. This blood will be tested for complete blood count, blood chemistry, and antibodies to darbepoetin alfa. We will perform electrocardiography.

- **Additional Withdrawal Visit** (28±2 days after you have been excluded). During this visit, your doctor will ask you questions about your health and will carefully examine you. He/she will measure your temperature, heart rate, blood pressure, height, and body weight. He/she will also examine your body. We will draw 10 mL of blood from your vein. This blood will be tested for complete blood count, blood chemistry, and antibodies to darbepoetin alfa. We will perform electrocardiography.

**Contraception** If you are able to have children, then for your own safety you should use effective birth control methods during the whole research period, from the screening examination and up to four weeks after you have received the last dose of the study drug. This means that you
should use a barrier contraceptive while your partner is using spermicide or oral contraceptive pills.

**IS THE STUDY DRUG SAFE?**

During this research, we will perform several standard medical procedures: for example, we will measure your blood pressure, perform electrocardiography, chest X-ray, and echocardiography. These are standard procedures and they are safe for you. When we draw blood from your vein, you may feel pain or get a bruise at the needle site, your skin above the vein may turn red, or you may feel dizzy. We will take your blood for testing several times during the research. The research study will last for about a year. During this period, we will draw not more than 142 mL of your blood. This is less than the amount of blood people usually donate. It is safe for you to lose this amount of blood within a year.

Treatment with the test drug and the reference drug may cause unwanted effects. Here you can find a list of unwanted effects that developed in patients with chronic kidney disease during treatment with the original drug containing darbepoetin alfa. These effects may occur in those receiving BCD-066 in this research study because BCD-066 also contains darbepoetin alfa.

**Blood and lymphatic system disorders**

Unknown frequency: red cell aplasia, which is a condition in which the bone marrow stops making red blood cells (erythrocytes) and their immature forms (reticulocytes), causing severe anemia.

**Nervous system disorders**

Common: stroke.

Uncommon: convulsions.

**Cardiac and vascular disorders**

Very common: blood pressure increased.

Uncommon: blocking of a blood vessel by a clot.

**Immune system disorders**

Very common: allergic reactions.

**Skin and subcutaneous tissue disorders**

Common: rash, skin reddening.

**General disorders and administration site conditions**

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1 We used the following frequency groups: very common (>1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000).
Common: pain at the injection site.

Patients treated with Aranesp® most often experienced allergic reactions (for example, rash), reactions at the injection site (skin reddening), and high blood pressure.

In the research study of BCD-066 in healthy volunteers, most common unwanted effects included abnormal blood tests (for example, decreased or increased white blood cells, decreased or increased neutrophils, decreased or increased platelets, increased monocytes, increased eosinophils). These abnormalities did not last for long, were found after injections of BCD-066 and Aranesp® with the same frequency and did not worsen volunteers’ health. There were rare cases of abnormal blood chemistry tests (for example, increased ALT, AST, or creatinine).

Your study doctor will be looking after you carefully during the study (from the first injection of the test drug or the reference drug and up to at least 28 days after the last injection). If any unwanted effect occurs, he/she will immediately help you. If it is necessary, you will be excluded from the research. If you feel unwell, please contact your study doctor as soon as possible.

**Use During Pregnancy and Lactation**

It is unknown whether BCD-066 may or may not cause harm to an unborn baby or a breastfed child. Pregnant and breastfeeding women cannot take part in this research study. Before you start participating in the research, we will ask you to confirm that, as far as you know, you are not pregnant and do not plan pregnancy during the entire research period. If there is a chance that you can get pregnant during the research period, your study doctor will recommend you effective birth control methods. If you think that you have become pregnant, please contact your study doctor and tell him/her that there is a chance you are pregnant. If this is true, you cannot continue your participation in this study and you will be excluded. Your doctor will monitor you during pregnancy and for six months after the baby has been born. Your study doctor will call you to ensure that you and your baby are safe.

**Male Sexual Problems**

The effects of the drug on the male reproductive system have not been studied. In animals, the drug did not cause any sexual problems.

**BENEFITS YOU GET FROM BEING IN THE STUDY**

Anemia in chronic kidney disease develops because damaged kidneys cannot produce enough erythropoietin. If you have this type of anemia, you cannot recover without treatment. Recombinant erythropoietins, produced using genetic engineering, are safe and effective drugs for
the treatment of CKD-related anemia. We expect that hemoglobin and red blood cell levels will return to their normal range (we call it a therapeutic success) with the same frequency in both research groups. First-generation recombinant erythropoietins maintain a normal hemoglobin level in the blood. Their drawback is that most patients have to inject them thrice a week. Darbepoetin alfa has similar efficacy but can be injected only once a week.

If you agree to take part in this study, you will receive treatment that maintains normal levels of hemoglobin and red blood cells and prevents you from developing symptoms of anemia. This will improve quality of your life, your ability to work, and your well-being. The research treatment will also reduce your need for blood transfusions and the risk of severe complications or death. Darbepoetin alfa will be injected only once a week instead of three times a week.

BCD-066 developed by JSC BIOCAD has been tested in non-clinical studies and a clinical study with healthy volunteers. Those studies showed that BCD-066 and Aranesp® had the same characteristics. That is why we expect that our drug will be as effective and as safe in patients with anemia as the original drug. In this research, we will use BCD-066 and Aranesp® to treat anemia caused by chronic kidney disease in patients on hemodialysis. Because BCD-066 was equivalent to Aranesp® in healthy volunteers, we expect it to be effective in this indication.

The treatment regimens used in this study have proved effective and safe in your disease, so their use in this research is ethically justified.

However, we cannot guarantee that your disease will improve during the research or that it will not worsen. If your disease worsen, your doctor may prescribe you any treatment that he/she believes to be effective.

You should know that there are other methods of treatment for CKD-related anemia but there is no clear evidence that they are more effective than darbepoetin alfa.

**PAYMENTS AND OTHER COMPENSATIONS FOR BEING IN THE STUDY**

You will not be paid for participating in this research study. Your participation in the research will not cause you any additional expenses.

During this research, you will be insured as a participant in a clinical study, according to the laws of the Russian Federation. You will be insured by Ingosstrakh Insurance Company (12, building 2, Ulitsa Pyatnitskogo, Moscow, Russia, 117997, Telephone: +7(495) 956-55-55). Your study doctor will give you a copy of the Insurance Contract and will tell you about its provisions (including your duties during this research).
Your study doctor will hand you your Compulsory Life and Health Insurance Policy for the participant in a clinical study. If you need to introduce changes into your Compulsory Insurance Policy, you will have to return the policy given you before. It will be exchanged for a new one within two working days.

The Insurance Policy covers claims of participants in the study to the Insurer only in terms of the compensation for harm to life and health caused by the participation in clinical studies, due to drawbacks of study drugs, or insufficient information about them, bolstering error or neglect. The insurance policy covers only those claims that are first asserted to the Insurer within the insurance period, concern events occurred in the insurance territory after the initiation of the study and are associated with the performance of the insured activity (the study).

If the study drug or a protocol-required medical procedure causes harm to your health, you will receive sufficient qualified medical care paid by the insurance company. Please note that the insurance company will pay for the research-related injury only if you follow all the instructions of your study doctor.

Your life and health will be insured under the Compulsory Insurance Contract of a participant in a clinical study. You will be insured from the moment you have signed the Informed Consent Form. Your study doctor will have to fill out (put your identification code) and hand you your Individual Compulsory Life and Health Insurance Policy of the participant in the clinical study. This Insurance Policy has a unified form in the Russian Federation. It is attached to this Information Sheet (you may also find the insurance terms attached to the Insurance Policy). If you need to introduce changes into your Compulsory Insurance Policy, you will have to return the policy given you before. It will be exchanged for a new one within two working days.

The Insurer is obliged to pay the following sums assured according to the Compulsory Insurance Contract (insurance payment):

1. If the insured person dies: 2 million Russian rubles. This sum insured is divided equally among all beneficiaries.

2. If the harm to the insured person’s health results in:
   - Group I disability: 1.5 million Russian rubles;
   - Group II disability: 1 million Russian rubles;
   - Group III disability: 500 thousand Russian rubles.

3. If the harm to the insured person’s health does not result in disability: not more than 300 thousand Russian rubles.
In the Russian Federation, the insurer pays the insurance benefit within 30 days from the date when an application of the insured person and all necessary documents have been received.

You will not be provided with another treatment and/or another compensation apart from the described above in case of death or harm to the health. This research does not involve optional health insurance.

Your participation in this research may violate the terms of your Optional Health Insurance Policy (if any), and you may lose your right to receive medical care provided by the optional medical insurance. If you have an Optional Health Insurance Policy, carefully study its provisions, limitations and restrictions before you decide to take part in this research.

WITHDRAWAL FROM THE RESEARCH FOR MEDICAL REASONS

If your study doctor believes that it meets your interests, he/she may withdraw you from the research at any time even if you do not agree (for example, because you have a serious adverse effect, or you do not follow your doctor’s prescriptions). If this happens, your study doctor will explain you the reason for withdrawal and provide you with further treatment.

HOW WILL YOUR RIGHTS BE PROTECTED DURING THE STUDY?

This research study is conducted in accordance with the laws of the Russian Federation, Russian National Standards, and international guidelines on studies of medicinal products for human use. Russian regulatory authorities have carefully considered this research study, its relevance, risk/benefit ratio, ethics, and have approved its conduct.

QUESTIONS AND CLAIMS

During the research period, the study doctor will give you all the new information that may make you change your mind about being in the study. Please feel free to contact your study doctor or the principal investigator if you have any questions or claims related to this research or if you want to have more information about this research or your rights as a participant.

CONFIDENTIALITY

You have the right to keep confidentiality. Nothing that could reveal your identity will be disclosed outside the study center unless otherwise provided by the law. Your medical records, including source documents, containing data that may reveal your identity will not be shared with
or given to anyone except 1) authorized representatives of JSC BIOCAD (monitors), 2) representatives of the Local Ethics Committee or Ethics Review Board that will monitor this research, and 3) regulatory authorities, as this is required by Russian and international laws. Information about your health will be processed. This means it may be collected, arranged, analyzed, saved, stored, updated, amended, distributed, and destroyed. Distribution of the information involves either publishing the research results or sharing your data with the above-mentioned authorities when it is required by the law. The published results of this research will not reveal your identity.

Information about your health will not be shared with insurance companies unless it is required by the law or you have given your written consent to do this.

Please contact your study doctor if you want to know what medical information can be given to the above-mentioned authorities. If you do not want us to use your data, please do not take part in this research. Even if you have already signed the Informed Consent Form, you may change your mind and decide that you do not want us to use your confidential data and may stop participating in this research at any time you wish. If you have changed your mind about being in the study, please contact your study doctor. If this happens, you will be withdrawn from the study. This will not affect the quality of medical care you are getting at the moment or will get at any time in the future.

If you agree to participate in this research, please sign below. You will be given a signed and dated copy of the Patient Information Sheet with the Informed Consent Form printed on 22 pages.
CONTACTS

Please keep this document in case you need to refer to it at a later time.

**Ethics Review Board of the Ministry of Healthcare of the Russian Federation:**

*Address and directions:* 3, Rakhmanovskiy Pereulok, Moscow, Russia, 127994. The nearest subway stations are “Tsvetnoy Bulvar”, “Trubnaya”, and “Chekhovskaya”.

*Chairperson of Ethics Review Board:* Professor Aleksandr Grigoryevich Chuchalin, Academician of the Russian Academy of Medical Sciences (RAMS). Tel: +7 (495) 625-44-21

**Study Center**

*Address and directions*

____________________________________________________________________________

Name of the Study Doctor, telephone

____________________________________________________________________________

Full name of Principal Investigator

____________________________________________________________________________

**Local Ethics Committee**

*Address*

____________________________________________________________________________

Name of Chairperson of Local Ethics Committee, telephone

____________________________________________________________________________

**Study Sponsor: JSC BIOCAD**

<table>
<thead>
<tr>
<th>Address of location: 34 A, Ulitsa Svyazi, Strelna, Petrodvortsoviy District, Saint Petersburg, Russia, 198515</th>
<th>Address for correspondence: Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tel: +7 (812) 380 49 33</td>
<td>Tel: +7 (495) 992-66-28</td>
</tr>
<tr>
<td>Fax: +7 (812) 380-49-34</td>
<td>Fax: +7 (495) 992-82-98</td>
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</table>

Working hours: 9:30–18:00 daily, except weekends and public holidays.
INFORMED CONSENT FORM

FOR PARTICIPATION IN A CLINICAL STUDY

A Multicenter, Double-Blind, Randomized, Comparative, Parallel-Group Clinical Study of the Efficacy and Safety of BCD-066 (JSC BIOCAD, Russia) and Aranesp® (Amgen Europe B.V., the Netherlands) in the Treatment of Anemia in Hemodialysis Patients with Impaired Kidney Function

I, __________________________________________

(full name of participant)

have got all the details on this research study from the study doctor __________________________________________

(full name of investigator)

about all aspects of the planned research study.

I have been informed about the purpose and course of the research study, the study drug, its expected efficacy and safety, benefits and risks of participating in this research, and my rights and duties as a participant. I have been warned about possible discomfort, adverse and side effects and my actions if any unforeseen effect occurs when I receive the study drug.

I have had the opportunity to ask the study doctor all the questions I wished, and I am satisfied with the answers.

I have been informed that I will take part in the research only if the full examination, performed according to the research protocol, shows that my state of health allows me to be in this research.

I have been told that my participation in this research is voluntary and that I am free to withdraw at any time without my medical care being affected.

I agree to follow the study doctor’s instructions, cooperate with him/her, and immediately inform him/her about any health problem should any arise.

I have been informed that if the study drug directly causes harm to my health, I will get all necessary medical care.
I sign the Informed Consent Form and give my permission to use and disclose confidential information about my health to the extent provided in the Confidentiality section of the Patient Information Sheet.

I confirm that before signing the Informed Consent Form I have read the Patient Information Sheet. I have received detailed and clear information from the Patient Information Sheet and the study doctor.

I confirm that I have been given enough time and information (including answers to my questions) to decide whether or not I wish to take part in this research.

I have been given a copy of the signed and dated Patient Information Sheet and the Informed Consent Form printed on 22 pages with an original Insurance Policy and its terms attached separately.

Print patient name

_____________________________________________________________________________

_____ Date __ __/ __ __/ __ __ __ Signature /__________________/

Print name of study doctor/person taking the consent

_____________________________________________________________________________

_____ Date __ __/ __ __/ __ __ __ Signature /__________________/
