



Thank you for your interest in participating in this clinical study. The document you are reading will give you information about the study you are going to take part in. You will be part of this research only if you give your consent and if the study doctor decides that you qualify to be in the study. Please ask the study doctor or the study team if you have any questions after reading this document, or if you are unclear about any part of the provided information. Do not sign the Informed Consent Form until you get satisfying answers to all your questions and decide that you want to participate in this study.

You are being invited to take part in a randomized, double-blind clinical study of the pharmacokinetics<sup>1</sup>, pharmacodynamics<sup>2</sup>, tolerability, and safety of darbepoetin alfa (product code BCD-066) manufactured by JSC BIOCAD (Russia) and Aranesp<sup>®</sup> manufactured by Amgen Europe B.V. (the Netherlands) given as multiple intravenous injections in healthy volunteers.

## **STUDY RELEVANCE**

Darbepoetin alfa is a common drug for anemia. It has been used for many years in patients with cancer or chronic kidney disease. Darbepoetin alfa normalizes the number of red blood cells (called erythrocytes). This improves oxygen transport from the blood into cells and normalizes the metabolism in the body.

Russian company JSC BIOCAD has developed its own drug containing darbepoetin alfa (product code: BCD-066). Physicochemical studies of BCD-066 (darbepoetin alfa made by BIOCAD) in laboratory animals showed that the drug produces specific effects on the bone marrow (particularly, it considerably increases the number of red blood cells and hemoglobin) and is not toxic. These results have proved that darbepoetin alfa is low-toxic and can be recommended for human research.

JSC BIOCAD has already tested BCD-066 in humans. It was given to healthy volunteers. The volunteers received one injection in their vein or under the skin. We tested BCD-066 to find out whether it stimulates the production of red blood cells (RBCs) and immature RBCs called reticulocytes. These are the cells preventing us from anemia (a condition when you have low hemoglobin). 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

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<sup>1</sup> Pharmacokinetics is how the drug moves in the body.

<sup>2</sup> Pharmacodynamics is how the body reacts to drugs.

reticulocyte levels between volunteers treated with BCD-066 and those treated with Aranesp<sup>®</sup>, which is the original darbepoetin alfa. BCD-066 is a biosimilar (biological copy) of Aranesp<sup>®</sup>. Both drugs had similar pharmacokinetics regardless of how they were injected. 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 the volunteers felt well and did not have complaints. Unwanted effects were similar after injections of BCD-066 and Aranesp<sup>®</sup>. Altogether, this information proves that, if you decide to take part in this research study, the drug safety will be the same, whether you receive one drug or another.

The clinical study we invite you to take part in is conducted to prove that BCD-066 (JSC BIOCAD) and Aranesp<sup>®</sup> given as multiple injections into the vein have equivalent pharmacokinetics, pharmacodynamics, and safety in healthy volunteers.

## **INFORMATION ON THE DRUG THAT IS BEING TESTED**

Both drug products that are being tested, BCD-066 and Aranesp<sup>®</sup>, contain darbepoetin alfa<sup>®</sup> as an active ingredient. Aranesp<sup>®</sup> (Amgen) has proved its high efficacy in numerous large research studies. It is widely used in clinical practice.

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.

Darbepoetin alfa specifically binds erythropoietin receptors on the surface of red cell precursors. This stimulates the bone marrow to produce more red blood cells and release them into the blood.

Darbepoetin alfa is widely used to treat anemic patients with chronic kidney disease or cancer, or those who have anemia after having received chemotherapy.

We have compared BCD-066 with Aranesp<sup>®</sup>. Tests showed that the drugs had the similar structure and physicochemical properties. We have finished several non-clinical research studies that compared pharmacology and toxicology of BCD-066 and Aranesp<sup>®</sup>. In these research studies, BCD-066 and Aranesp<sup>®</sup> produced similar effects. We have also performed a comparative double-blind randomized study of the pharmacokinetics/pharmacodynamics and safety of BCD-066 and Aranesp<sup>®</sup>, each given as one subcutaneous injection. This study involved 74 healthy volunteers,

and BCD-066 and Aranesp<sup>®</sup> showed identical characteristics. As the first clinical study of BCD-066 in healthy volunteers showed good results, we are now studying its efficacy and safety upon repeated intravenous injections. This study is also conducted in healthy volunteers.

In this clinical study, you will receive 4 intravenous injections of 1.0 µg/kg darbepoetin (BCD-066 or Aranesp<sup>®</sup>). Injections will be given to you once a week.

### **PURPOSE AND OBJECTIVES OF THE RESEARCH STUDY**

This study is conducted for research purposes only (section 4.8.10 of the Russian National Standard GOST R 52379-2005).

The purpose of this research is to compare the pharmacokinetics (how the drug is distributed over the body), pharmacodynamics (what biological effects the drug produces in the body), tolerability, and safety of BCD-066 (JSC BIOCAD) and Aranesp<sup>®</sup> in healthy volunteers.

### **WHO ORGANIZES THE STUDY? WHAT INSTITUTIONS ARE INVOLVED?**

This study has been initiated and is sponsored by JSC BIOCAD, a Russian biotechnological company. The company was founded in 2001, and it carries out research activities and manufactures drug products. 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 a healthcare center certified for conducting clinical studies as required by law.

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

Your participation in this research is voluntary. You can take part in this research if you have signed the Informed Consent Form and meet the following criteria:

1. You are a male
2. You are 18 to 45 years old (inclusive)
3. Your body weight is in the normal range
4. The study doctor confirms that you are healthy (based on the information from talking to you, physical examination, and lab tests)

5. Certain values in your blood test (hemoglobin, transferrin, ferritin, Vitamin B12, folic acid, and endogenous erythropoietin) fall within the normal ranges
6. You agree to use effective birth control methods during the screening (14 days before you start participating in this research) and for 28 days after the last injection of the study drug.
7. You agree not to drink alcohol within 24 h before each injection of the study drug and for 72 h after it.
8. Your general health was good for 30 days before enrollment

You cannot take part in this research if any of the following is true:

1. You have clinically significant ECG or laboratory abnormalities at screening that potentially can affect your safety if you participate in this research
2. You had an illness within four weeks before the screening
3. You had or now have cancer
4. Some of your laboratory or instrumental test results fall outside the normal ranges
5. You have any chronic cardiovascular, bronchial and/or pulmonary or neuroendocrine disorders; or you have any disease of the gastrointestinal tract, liver, kidneys or blood, coronary disease, arterial hypertension, or any disease of your peripheral or cerebral vessels, or thrombocytosis
6. You already received drugs containing erythropoietin or darbepoetin or any other drugs promoting erythropoiesis (at any time before you are enrolled in this research)
7. You received intravenous therapy with iron-containing medications (within two years before you are enrolled in this research)
8. You used drugs, vitamins or nutritional supplements within 14 days before the first injection of the study drug. This does not apply to paracetamol (not more than 3 g a day) and ibuprofen (not more than 1 g a day)
9. You smoke more than 10 cigarettes a day
10. You donated your blood or plasma, or you had a bleeding within 2 months before enrollment
11. You had epileptic seizures within 6 months before the first injection of the study drug
12. You tested positive for HIV, hepatitis C and/or B

13. You have drug abuse or alcohol abuse problems. You drink more than 5 liters of beer or more than 2 liters of wine or more than 500 mL of strong alcohol drinks per week
14. An intravenous catheter cannot be inserted in your vein for blood sampling (e.g., because of a skin condition at the prick site)
15. You had a major surgery within one month before you are enrolled in this research.
16. You have had episodes of thrombosis (e.g., a heart attack, a stroke, a transient ischemic attack, deep vein thrombosis, or pulmonary embolism) within 6 months before enrollment
17. You have had chronic bleedings
18. The screening tests show that you have antibodies to darbepoetin alfa
19. You had or now have any strong allergy
20. You are intolerant to any component of BCD-066 (JSC BIOCAD), Aranesp<sup>®</sup> (Amgen Europe B.V., the Netherlands), or other drugs of this class; or you are intolerant to erythropoietin and/or other human recombinant proteins and/or iron (III)
21. Your study doctor thinks that you cannot take part in this research
22. You now participate in another clinical study or you participated in another study within 30 days before being enrolled in this study, or you already participated in this clinical study.

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

You may change your mind later and stop participating at any time. During the study, the study team will promptly tell you about any new information (if any) that may affect your safety or willingness to continue being in the study.

If you decide to prematurely stop being in the study, talk to your study doctor right away.

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 DIAGNOSTIC 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 (the test drug or the comparator) you will receive. This is also a randomized study, which means that the groups are selected by chance, as if by tossing a coin.

The research you are invited to take part in will involve 62 healthy male volunteers aged from 18 to 45 years old (inclusive). This includes 56 active participants and 6 backups to replace those who withdraw from the study. All participants will be randomly assigned (randomized) to one of two equal groups, 28 men in each. In one group, participants will be treated with BCD-066, while participants in another group will be treated with Aranesp<sup>®</sup>.

On Day 1, each participant will receive an intravenous injection of BCD-066 or Aranesp<sup>®</sup> at a dose of 1.0 µg/kg. Seven days later (on Day 8), participants will be given a second intravenous injection (BCD-066 or Aranesp<sup>®</sup>) at a dose of 1.0 µg/kg. Seven days later (on Day 15), participants will be given a third intravenous injection (BCD-066 or Aranesp<sup>®</sup>) at a dose of 1.0 µg/kg. Seven days later (on Day 22), participants will be given a fourth intravenous injection (BCD-066 or Aranesp<sup>®</sup>) at a dose of 1.0 µg/kg.

The interval between the injections will be 7 days.

Your study doctor will monitor you for another 28 days after you get the fourth injection of the study drug. The maximum duration of the study for you will be 64 days (14 days of the screening period and 50 days of active study and follow up).

To maintain sufficient iron levels in your body, the doctor will prescribe you a medication that contains iron (III). You will have to take this iron (III) medication (100 mg or 1 tablet) twice a day at least 4 hours apart. You will start taking your iron medication on Day 1 (Visit 1 when you get the first injection) and then will take it daily through Day 29 (Visit 16). Thus, you will be taking the iron (III) medication for 29 days. The iron (III) medications are well-established and widely used to treat iron-deficiency anemia in people of all ages. Iron (III) drugs may cause stool color changes and, less frequently, nausea and diarrhea. Both study drugs (the test drug and the comparator) and the iron supply medication will be provided by the sponsor of this research study (JSC BIOCAD). To monitor the amount of iron (III) medication taken, you will be asked to fill out a drug intake diary. Your study doctor will give you this diary during your first study visit. You will be asked to bring your diary with you at each visit, so your doctor could check whether you fill it out properly.

Before randomization, neither you nor your study doctor will know in which treatment group you will be placed.

After getting the first and the fourth injection of the study drug, you will spend 24 hours in the clinic. Your study doctor will look after you. During this research, you will make several visits to the clinic (study center). Your study doctor will tell you the exact dates of visits.

This research will include the screening, 16 visits to the clinic, and one telephone call.

You will have to arrive at the study center in the morning, at least two hours before the scheduled time of the injection.

An intravenous catheter (a needle) will be inserted in the vein in your arm. The catheter will remain in your arm for 24 hours. The catheter will be inserted only on the days when you receive injections.

During the first visit, some blood will be taken from your vein 30 min, 20 min, 10 min and immediately before the injection of the study drug. Then, you will receive an injection of the study drug. You will stay in the clinic for 24 h after the injection.

During the first 24 h after the injection, small amounts of blood will be collected from your vein according to the following schedule:

- 5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 1 h, 2 h, 4 h, 8 h, 16 h, and 24 h after the injection. We will use this blood to measure the drug concentration. Some blood will also be collected 48 h and 72 h after the injection.

Your study doctor will measure your blood pressure, pulse, body temperature, breathing rate, and evaluate your overall health. You will not be allowed to smoke for 1 h before and for 3 h after each injection and for 1 h before your blood pressure is measured. Always ask your study doctor about the timing of any upcoming procedures.

On Day 2 after the injection of the study drug, a study team member will remove the catheter from your arm. Your study doctor will measure your blood pressure, pulse, body temperature, and breathing rate. After this is done, you can leave the study center. However, you will have to come back to give a blood sample 48 h after the first infusion.

The interval between the injections will be 7 days. The visits cannot be re-scheduled.

After you receive the last injection of the study drug, you will be monitored for 4 more weeks (28 days). Your study doctor will give you a call on Days 34±2, 42±2 and 50±2 and ask you about your health.

Here you can find a brief description and timing of the study visits:

### **Screening (-14 days)**

1. You will sign the Informed Consent Form



2. Your doctor will interview you about your health
3. Your doctor will ask you about medications you take
4. Your doctor will perform a physical exam and measure your body weight and height
5. Your doctor will measure your blood pressure, pulse, and breathing rate
6. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test and test for psychoactive drugs/substances
7. Some blood will be taken from you to run a hematology test
8. Some blood will be taken from you to run a chemistry test (+ evaluate the markers of iron metabolism, vitamins, and endogenous erythropoietin)
9. A sample of your saliva will be tested for alcohol
10. An ECG will be recorded
11. Fluorography or chest X-ray will be performed if you have not done it in the previous 8 weeks
12. Some blood will be taken to test it for antibodies to darbepoetin alfa
13. Some blood will be taken to test it for the human immunodeficiency virus (HIV) Hepatitis B and C, and syphilis
14. Your study doctor will check whether you are eligible for the study
15. You will be assigned to one of two study groups
16. Your doctor will evaluate the safety

At screening, we will draw about 27 mL of blood from you.

### **Visit 1 (days 1-2)**

1. Your doctor will ask you about medications you take
2. Your doctor will perform a physical exam and measure your body weight
3. Your doctor will measure your blood pressure, pulse, and breathing rate before the injection of the study drug and then 1 h and 24 h after the injection
4. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test and test for psychoactive drugs/substances
5. A sample of your saliva will be tested for alcohol
6. You will take the iron (III) medication and fill out the drug intake diary\*
7. A venous catheter will be inserted in / removed from your arm

8. You will receive an injection of BCD-066/Aranesp<sup>®</sup>
9. Some blood will be taken from you to measure the concentration of the study drug  
Blood samples will be collected 30 min, 20 min, and 10 min before the injection, immediately before the injection, and 5 min, 10 min; 15 min, 20 min, 30 min, 45 min, 1 h, 2 h, 4 h, 8 h, 16 h, and 24 after the injection
10. The study doctor will examine the injection site before the injection and then 2 h and 24 h after the injection.
11. Some blood will be taken from you on Day 1 and Day 2 to run a hematology test

During Visit 1, we will draw about 134 mL of blood from you.

### **Visit 2 (Day 3)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to measure the concentration of the study drug
4. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 2, we will draw about 8 mL of blood from you.

### **Visit 3 (Day 4)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to measure the concentration of the study drug
4. Blood samples will be taken from you to run a hematology and chemistry tests
5. to provide a sample for a comprehensive urine test
6. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 3, we will draw about 14 mL of blood from you.

### **Visit 4 (Day 6)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to run a hematology test

4. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 4, we will draw about 3 mL of blood from you.

**Visit 5 (Day 8)**

1. Your doctor will ask you about medications you take
2. Your doctor will perform a physical exam and measure your body weight
3. Your doctor will measure your blood pressure, pulse, and breathing rate once before the injection and then 1 h after the injection of the study drug
4. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test and test for psychoactive drugs/substances
5. A sample of your saliva will be tested for alcohol
6. A blood sample will be taken from you to measure the concentration of the study drug before the second injection
7. One blood sample will be taken from you to run a hematology test
8. You will take the iron (III) medication and fill out the drug intake diary\*
9. A venous catheter will be inserted in / removed from your arm
10. Your doctor will examine the injection site before and 2 h after the injection
11. You will receive an injection of BCD-066/Aranesp<sup>®</sup>

During Visit 5, we will draw about 11 mL of blood from you.

**Visit 6 (Day 9)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. Your doctor will examine the injection site 24 h after the injection
4. One blood sample will be taken from you to run a hematology test
5. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 6, we will draw about 3 mL of blood from you.

**Visit 7 (Day 11)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate

3. Blood samples will be taken from you for hematology and chemistry tests and the test for iron metabolism
4. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test
5. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 7, we will draw about 9 mL of blood from you.

**Visit 8 (Day 13)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to run a hematology test
4. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 8, we will draw about 3 mL of blood from you.

**Visit 9 (Day 15)**

1. Your doctor will ask you about medications you take
2. Your doctor will perform a physical exam and measure your body weight
3. Your doctor will measure your blood pressure, pulse, and breathing rate before and 1 h after the injection
4. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test and test for psychoactive drugs/substances
5. A sample of your saliva will be tested for alcohol
6. A blood sample will be taken from you to measure the concentration of the study drug before the third injection
7. One blood sample will be taken from you to run a hematology test
8. You will take the iron (III) medication and fill out the drug intake diary\*
9. A venous catheter will be inserted in / removed from your arm
10. Your doctor will examine the injection site before and 2 h after the injection
11. You will receive an injection of BCD-066/Aranesp<sup>®</sup>

During Visit 9, we will draw about 11 mL of blood from you.

**Visit 10 (Day 16)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to run a hematology test
4. Your doctor will examine the injection site 24 h after the injection
5. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 10, we will draw about 3 mL of blood from you.

**Visit 11 (Day 18)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. Blood samples will be taken from you for hematology and chemistry tests and the test for iron metabolism
4. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test
5. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 11, we will draw about 9 mL of blood from you.

**Visit 12 (Day 20)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to run a hematology test
4. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 12, we will draw about 3 mL of blood from you.

**Visit 13 (Days 22-23)**

1. Your doctor will ask you about medications you take
2. Your doctor will perform a physical exam and measure your body weight
3. Your doctor will measure your blood pressure, pulse, and breathing rate before the injection of the study drug and then 1 h and 24 h after the injection
4. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test and test for psychoactive drugs/substances
5. A sample of your saliva will be tested for alcohol

6. You will take the iron (III) medication and fill out the drug intake diary\*
7. A venous catheter will be inserted in / removed from your arm
8. You will receive an injection of BCD-066/Aranesp<sup>®</sup>
9. Some blood will be taken from you to measure the concentration of the study drug  
Blood samples will be collected 30 min, 20 min, and 10 min before the injection, immediately before the injection, and 5 min, 10 min; 15 min, 20 min, 30 min, 45 min, 1 h, 2 h, 4 h, 8 h, 16 h, and 24 after the injection
10. Two blood samples will be taken from you (one sample on each Day 22 and Day 23) to run a hematology test
11. The study doctor will examine the injection site before the injection and then 2 h and 24 h after the injection.

During Visit 13, we will draw about 134 mL of blood from you.

**Visit 14 (Day 24)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to measure the concentration of the study drug
4. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 14, we will draw about 8 mL of blood from you.

**Visit 15 (Day 25)**

1. Your doctor will ask you about medications you take
2. Your doctor will measure your blood pressure, pulse, and breathing rate
3. One blood sample will be taken from you to measure the concentration of the study drug
4. Blood samples will be taken from you for hematology and chemistry tests and the test for iron metabolism
5. You will be asked to urinate in a cup to provide a sample for a comprehensive urine test
6. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 15, we will draw about 17 mL of blood from you.

**Visit 16 (Day 29)**

1. Your doctor will ask you about medications you take
2. Physical examination
3. Your doctor will measure your blood pressure, pulse, and breathing rate
4. One blood sample will be taken from you to run a hematology test
5. Some blood will be taken to test it for antibodies to darbepoetin alfa
6. You will take the iron (III) medication and fill out the drug intake diary\*

During Visit 16, we will draw about 5 mL of blood from you.

\* You will be taking an iron (III) medication and fill out the drug intake diary every day starting from the day of the first injection of BCD-066/Aranesp<sup>®</sup> (Day 1, Visit 1) and through Day 29 of the study (Day 29, Visit 16).

**Days 34±2, 42±2, and 50±2.** You will communicate with your study doctor via phone calls.

You will be in the study for 50 days from the first injection of the study drug. Over the first 29 days, you will need to come to the study site 16 times, and then talk to your study doctor by phone three times.

If you develop any side effects, your study doctor may refer you to additional tests, extend the duration of your stay in the clinic, or ask you to come for an additional examination. If you feel any changes in your health or feel unwell, talk to your study doctor right away.

**SPECIAL RECOMMENDATIONS TO STUDY PARTICIPANTS**

You should know that you will be withdrawn (removed) you from the research if you miss at least one of the study drug injections. Please note that the study visits cannot be re-scheduled.

If you consent to take part in the study, you will be not allowed to:

- Take any food at least 8 h before the scheduled blood sampling for hematology and chemistry testing
- Smoke within 1 h before and for 3 h after each injection and within 1 h before each blood pressure measurement

- Consume alcohol within 24 h before and for 72 h after each injection of the study drug.

You should not take any medications (including over-the-counter medications, nutritional supplements, vitamins, and homeopathic products) before you get an approval from your study doctor. If you need to take any new medication, please contact your study doctor as soon as possible. The study doctor will tell you whether you can or cannot use this new drug while you are participating in this research and will give appropriate recommendations.

Please tell 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 need to carefully follow all rules and procedures prescribed by the study doctor and set by the study protocol. You agree to report all changes in your health whether or not they are related to the study products.

### Contraception

If you and your sex partner are technically able to have children, then for your safety you must use effective birth control methods during the entire research period, starting 2 weeks before you are enrolled in the study 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 (e.g a condom) together with one of the following: spermicides, intrauterine device or birth control pills. You should also make sure that your sex partner also uses appropriate contraception measures during the said period.

## **IS THE STUDY DRUG SAFE?**

During this research, we will perform several standard medical procedures. For example, we will measure your blood pressure and draw blood from your vein.

The effects of BCD-066 (darbepoetin alfa made by JSC BIOCAD) have been studied in laboratory animals and in healthy volunteers. BCD-066 is a biological copy (biosimilar) of the known and widely used drug Aranesp<sup>®</sup>. It has been shown that Aranesp<sup>®</sup> and BCD-066 produce similar effects on the body (bone marrow, liver, and spleen) and are both non-toxic. That is why



we assume that the risk of adverse events (unwanted effects) when you use BCD-066 is minimal and is similar to the risk of adverse events when you use Aranesp<sup>®</sup>.

The following unwanted reactions were observed in clinical studies of darbepoetin (Aranesp<sup>®</sup>):

1. Cardiac and vascular disorders:
  - Increased blood pressure or worsening of existing hypertension.
  - Thrombi (blood clots) in blood vessels (including large vessels).
2. Nervous system disorders: headache.
3. Blood and lymphatic system disorders: temporary increase in the platelet count.
4. Investigations: low ferritin (a protein that stores and releases iron), occasional high phosphorus and potassium in the blood.
5. Other: flu-like syndrome (high body temperature, pain in bones and joints), allergy, anaphylactic shock.

The intravenous catheter that will be inserted into your vein also may cause some unwanted effects: you may feel pain or get a bruise at the needle site, your skin above the vein may turn red, or you may feel weak. On some visits, blood samples will be drawn using disposable (single-use) syringes.

You should be particularly careful while operating heavy machinery or driving a car on the day when you get an injection of Aranesp<sup>®</sup> or BCD-066 because these drugs may suddenly increase your blood pressure and reduce your alertness.

During your participation in the study, members of the study team will do certain manipulations, e.g. measure your blood pressure, record your ECG, take blood samples from your vein, etc.. All these activities will be performed according to the standard procedures and are safe for you.

During the study, multiple blood samples will be taken from you for various tests. The amount of blood that will be taken from you over 29 days of the study will not exceed 29 mL. This is less than the amount of blood people usually donate at one time. It is safe for you to lose this amount of blood. When blood is taken from your vein, you may feel some pain or get a light bruising, but the risk of such reactions is not higher than if you receive an intravenous injection not in a clinical study but as part of a routine medical care. A chest X-ray or fluorography will be performed at screening. This test will be skipped if you provide the results of such an examination

performed within 2 months before screening. These tests involve some X-ray radiation, yet it is so low that has no effect on your health.

Your study doctor will monitor you carefully during the study (starting from the first injection of BCD-066 or Aranesp<sup>®</sup> and for at least 28 days after the last injection). If any unwanted effect occurs, your study doctor will immediately help you. If it is necessary, you will be taken off the research. If you feel unwell, please contact your study doctor as soon as possible.

Inform your study doctor or the Local Ethics Committee (see CONTACTS section below for contact details) about any disturbing changes in your health state.

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

This research will not improve your health, but you will get a free medical examination.

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

Each study participant will be paid 45 000 (forty five thousand) Russian Rubles. Payments will be made in cash at the study site or by a wire transfer to the subject's bank account within 7 (seven) working days from the day when the subject has completed the study. You will be paid only if you complete this clinical study according to the schedule (i.e. if you will perform all the study procedures and attend all the study visits).

The Sponsor will not provide any special compensation for your travel to the study center or other expenses. If for your own safety or for other reason, your study doctor recommends you an additional examination or advises you visiting another doctor, BIOCAD will not pay for such examination or visit. The compensation is subject to taxation according to the law of the Russian Federation.

During this research, you will be insured as a clinical study participant according to the laws of the Russian Federation. You will be insured by SPAO Ingosstrakh (12, building 2, Pyatnitskaya Ul., Moscow, Russian Federation, 117997 Tel.: +7(495) 956-55-55).

The study doctor will give you a copy of the Insurance Agreement and explain you its terms and conditions (including the responsibilities of volunteers participating in the study). Your life and health will be insured under the Agreement on Compulsory Insurance of the life and health of a subject participating in a drug clinical study. You will be insured from the moment you sign the Informed Consent Form.

Your study doctor will have to fill out (put your individual identification code) and hand you your Individual Compulsory Life and Health Insurance Certificate for the participant in a clinical study. The form of a compulsory insurance certificate is identical all over the Russian Federation and is a mandatory attachment to this Information Sheet. An explanation of insurance terms conditions may be attached here as well. If you need to make any changes to the compulsory insurance certificate, you should return the previously issued certificate and receive a new one within 2 working days.

The Insurance Certificate covers claims of participants in the study to the Insurer (BIOCAD) 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 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 you are injured due to the study drug, you will receive all the necessary medical care. You will not need to pay for this care; it will be 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 given to you by your study doctor.

The Insurer shall pay the following compensations according to the Compulsory Insurance Contract (insurance payment):

If the insured person dies: 2 million Russian Rubles. This insurance payment is divided equally among all beneficiaries.

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: 500 000 Russian Rubles.

If the harm to the insured person's health does not result in disability: not more than 300 000 Russian Rubles.

The Insurer pays the compensation within 30 days from the date when the insurance company receives an application from the insured person and all the required documents.

This study does not provide any other options for treatment and/or compensation in case of research-related death or injury. This study will not provide any private (voluntary) health insurance schemes.

Participation in this clinical study may violate the terms of your private (voluntary) medical insurance (if any) and deprive you of your right for medical care provided by this private (voluntary) medical insurance. Therefore, if you have a valid private medical insurance policy, read carefully its terms and conditions before making your decision about participating in this study.

### **WITHDRAWAL FROM THE STUDY FOR MEDICAL REASONS**

If your study doctor believes that it meets your best 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 to you the reason for withdrawal and provide you with further treatment if needed.

### **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 reviewed this research study, its feasibility, risk/benefit balance, and ethics, and have approved its conduct.

### **QUESTIONS AND CLAIMS**

You will be immediately informed about any new information that could affect your willingness to continue being in the study. If you have any questions or claims related to the study, or if you would like to get more information about the study or about your rights in the study, do not hesitate to contact your study doctor or the principal investigator.

### **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 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: collected, arranged, analyzed, accumulated,

stored, updated/modified, distributed, and destroyed. All people who will have access to your personal data will keep them confidential as required by the current law. Distribution of the information involves either publishing the research results or sharing your data with the above-mentioned authorities when it is required by law. The published results of this research will not reveal your identity.

The study doctor will anonymize all the information obtained in the study, including medical information that will be sent to the Sponsor. This information will be protected with a unique code assigned to you at the beginning of the study. The Sponsor will store this anonymized information (both printed and electronic copies) for a specified period of time. It can be used in analyzing study results, preparing study reports and scientific articles, or obtaining an approval for the drug to be marketed.

Any other disclosure of information obtained in this study, including your medical information, to third parties is permitted only when required by law or when your information has already been anonymized.

Your medical information will not be disclosed to insurance companies unless required by law or unless you give a separate written consent.

If you change your mind and decide to stop being in the study, the Sponsor has the right to use your information that has been obtained by the time of your withdrawal.

If you have any questions about specific medical information that can be disclosed to the above-mentioned authorities, please do not hesitate to ask the study doctor.

By agreeing to be in the study and by signing this Informed Consent Form you confirm that you have been told about how your information will be treated, and you permit direct access to your medical information under the specified conditions.

**If you agree to participate in this research, please sign below. You will receive a signed and dated copy of the Information Sheet with the Informed Consent Form on 24 pages.**

## CONTACTS

**Please keep this document until the end of the study.**

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

**Address and directions:** 3, Rakhmanovskiy per., Moscow, Russian Federation, 127994. The nearest subway stations: Trubnaya, Tsvetnoy Bulvar, 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**

\_\_\_\_\_  
**Name of the Principal Investigator**

\_\_\_\_\_  
**Local Ethics Committee**

**Address** \_\_\_\_\_

\_\_\_\_\_  
**Name of Chairperson of Local Ethics Committee,  
telephone** \_\_\_\_\_

\_\_\_\_\_  
**Study Sponsor: JSC BIOCAD**

<b>Located at:</b> 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russia, 198515 Tel.: +7 (812) 380-49-33 Fax: +7 (812) 380-49-34	<b>Address for correspondence:</b> Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russia, 143422 Tel.: +7 (495) 992-66-28 Fax: +7 (495) 992-82-98
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Working hours: 9:30–18:00 daily, except weekends and public holidays.

**INFORMED CONSENT FORM  
FOR PARTICIPATION IN CLINICAL STUDY**

**A Double-blind, Randomized, Controlled Clinical Study of the Pharmacokinetics,  
Pharmacodynamics, Tolerability, and Safety of Multiple Intravenous Injections of BCD-  
066 (JSC BIOCAD) and Aranesp® (Amgen Europe B.V., the Netherlands) in Healthy  
Volunteers**

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 clinical 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 the 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 the 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 Participant Information Sheet.

I confirm that before signing the Informed Consent Form I have read the Participant 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 Information Sheet and Informed Consent Form printed on 24 pages with an original Insurance Certificate and its terms attached as a separate document.

Print name of the participant

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Date \_\_\_/\_\_\_/\_\_\_ Time \_\_\_ h / \_\_\_ min Signature / \_\_\_\_\_/

Print name of the investigator (do not abbreviate) who performed the consent process/physician's personal seal

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Date \_\_\_/\_\_\_/\_\_\_ Time \_\_\_ h / \_\_\_ min Signature / \_\_\_\_\_/