CLINICAL STUDY PROTOCOL

Protocol Title:	An International, Multicenter, Randomized, Open-Label, Comparative Clinical Study of the Efficacy and Safety of BCD-131 (JSC BIOCAD, Russia) and Mircera® (F. Hoffmann-La Roche Ltd, Switzerland) in the Treatment of Anemia in Dialysis Patients with Chronic Kidney Disease
Protocol ID:	BCD-131-2, NCT03519243
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Protocol ID	BCD-131-2
Study Title	An International, Multicenter, Randomized, Open-Label, Comparative Clinical Study of the Efficacy and Safety of BCD-131 (JSC BIOCAD, Russia) and Mircera® (F. Hoffmann-La Roche Ltd, Switzerland) in the Treatment of Anemia in Dialysis Patients with Chronic Kidney Disease.
Phase	II
Study Sponsor	JSC BIOCAD Postal address: Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 Legal address: 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, Saint Petersburg, Russian Federation, 198515
Test drug	BCD-131 — pegylated darbepoetin (JSC BIOCAD, Russia), solution for injection.
Description of the Test Drug	BCD-131 is a covalent conjugate of darbepoetin with the low content of sialic acids and linear methoxy-polyethylene glycol with the molecular weight of 30 kDa. Pegylated darbepoetin is expected to have a longer half-life and higher *in vivo* activity than the available authorized drugs. As a result, the drug will be administered to patients less often, the blood concentration of the active ingredient will be more stable thus promoting further improvement of the patient's prognosis and quality of life. Pegylated darbepoetin (BCD-131) developed by JSC BIOCAD is an innovative biotechnology product. To date, a comprehensive study of structural, physico-chemical and biological properties of BCD-131 has been conducted. The amino acid profile, three-dimensional structure, sialylated form profile, purity and homogeneity, *in vivo* potency and stimulating activity of pegylated darbepoetin in TF-1 cells have been studied. The first step of clinical development of BCD-131 was the evaluation of its effects in healthy volunteers in the Phase I study: "Open-Label Single Ascending Dose Clinical Trial to Evaluate the Pharmacokinetics, Pharmacodynamics, Tolerability, Safety and Immunogenicity of BCD-131 in Healthy Volunteers as Compared to Mircera® (F. Hoffman-La Roche Ltd., Switzerland) and Aranesp® (Amgen Europe B.V., Netherlands)". According to the results of the Phase I study, the anticipated therapeutic dose range of BCD-131 was selected based on the evaluation of the drug pharmacodynamic (PD) effect on stimulation of erythropoiesis. The pharmacodynamic response reflected by the increased

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	reticulocyte count, which was very similar to that due to the comparator Mircera®, was observed in the cohorts of volunteers receiving BCD-131 at a dose of 1.05 µg/kg, 1.7 µg/kg, and 2.75 µg/kg. The further development of BCD-131 includes the study of its efficacy and safety for the treatment of renal anemia due to the end-stage chronic renal failure (CKD (chronic kidney disease) stage 5D) in epoetin or darbepoetin alfa-treated patients.
Reference Drug	Mircera® — methoxy polyethylene glycol-epoetin beta (F. Hoffmann-La Roche Ltd., Switzerland) solution for intravenous and subcutaneous injection.
Study Aims and Objectives	**Study aim:** To determine an effective and safe therapeutic dose of BCD-131 upon repeated administration of the drug to dialysis patients with chronic kidney disease treated for anemia. **Study objectives** 1. Determine and compare the efficacy variables of 3 different doses of BCD-131 upon multiple administration of the test drug with those of Mircera®. 2. Study and compare the adverse event profile of 3 different doses of BCD-131 upon multiple administration of the test drug with that of Mircera®. 3. Determine and compare the pharmacokinetics (PK) and pharmacodynamics (PD) of 3 different doses of BCD-131 upon multiple administration of the test drug with those of Mircera®. 4. Determine and compare the proportion of BAb- and NAb-positive patients in the BCD-131 and Mircera® groups.
Study Design	Clinical study BCD-131-2 is an international, multicenter, randomized, open-label, comparative two-stage clinical study to determine an effective and safe therapeutic dose of BCD-131 upon multiple administration of the drug to dialysis patients with chronic kidney disease treated for anemia. The study will include up to 100 dialysis patients with stage 5D chronic kidney disease (end-stage chronic renal failure), established efficacy of dialysis and renal anemia without other causes of anemia development (such as anemia of chronic disease, vitamin B12 deficiency, folic acid deficiency, iron deficiency), receiving erythropoiesis-stimulating agents (ESA) and reaching target hemoglobin levels. This study is a study of the maintenance

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	treatment of anemia; therefore, the study population includes patients: – receiving recombinant erythropoietin (EPO) (epoetin alfa or epoetin beta, or darbepoetin alfa) for at least 3 months before signing the Informed Consent (IC); – receiving a stable dose of recombinant EPO (epoetin alfa or epoetin beta, qw, biw, tiw, or darbepoetin alfa, qw or q2w) for at least 2 weeks before signing the Informed Consent and during the screening period; – with hemoglobin levels within target values (100-120 g/L) for at least 2 weeks before signing the Informed Consent and at screening. **Randomization and Stratification** The study plans to include 4 groups: 3 groups will receive the test drug BCD-131 at a dose of 1.05 µg/kg, 1.7 µg/kg and 2.75 µg/kg x conversion ratio (CR)[1] based on the previous therapy and one group will receive the reference drug Mircera®. Before inclusion in the study, all patients will be provided with the full information about the clinical study, its aims, and the risks associated with the participation in the study. After signing the Informed Consent, patients will undergo a screening examination (within the screening period of max 4 calendar weeks) to confirm that they meet the eligibility criteria. After the investigator has decided to include the patient in the study, they will be stratified based on the previous therapy (epoetin alfa / epoetin beta / darbepoetin alfa) and risk factors for AE development due to rHuEPO therapy: age (<60 years / ≥60 years), availability / absence of vascular implants, need/no need for hypoglycemic agents or insulin. **Study Stages:**

[1] The dose calculations for BCD-131 and Mircera® are provided in section "Study Therapy" of the Synopsys and in section 1.5.1 "Description and Justification of Administration Mode, Doses, Dosage Regimen and Treatment Course" of the Study Protocol.

Monthly doses of BCD-131 and Mircera® depend on a stable dose of recombinant EPO (epoetin alfa or epoetin beta, or darbepoetin alfa) received by the patient for at least 2 weeks before signing the Informed Consent and during the screening period.

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	The study will include the following two stages: **Stage I** At stage I, patients will be included successively in each of the groups to receive BCD-131. At the same time, patients will be included in the reference group to receive Mircera®. Patients will be included in the groups in a 3:1 ratio (BCD-131 group : Mircera® group). First, 9 patients will be included in Group 1 (BCD-131, 1.05 µg/kg x CR depending on the dose of the previous therapy) and 3 patients will be included in the Mircera® group (in a 3:1 ratio). After all the enrolled patients from these groups (Group 1 and the reference group) have received 2 injections of the test/reference drug and completed a 2-week follow-up period after the second injection (i.e. 1.5 months (42 days) after the first injection or 14 days after the second injection), the investigators will consider a possibility of including the next 9 patients in Group 2 (BCD-131, 1.7 µg/kg x CR depending on the dose of the previous therapy). At stage I, the Data Safety Monitoring Committee (DSMC) will take a decision on a possibility of including the next group of patients to receive a higher dose (1.7 µg/kg x CR)[2]. The decision will be based on the pooled data on the safety and pharmacodynamics of BCD-131 obtained in patients from Group 1 for the first 1.5 months (i.e. after two injections and a 2-week follow-up period after the second injection). The safety evaluation of the test drug will be based on the incidence of Grade 3 AEs, having a reasonable suspected causal relationship to the study drug (according to the DSMB), in patients from Group 1. To perform the preliminary evaluation of the PD effect of the indicated dose of the drug product, DSMC members will be additionally provided with the data on hemoglobin levels and reticulocyte counts in complete blood counts of the patients included in Group 1 at stage I. The treatment of patients in Group 1 at stage I and in the reference group will not be interrupted and continue according to the Study Protocol. After the DSMC members have taken a decision about further dose escalation, 9 patients will be randomized to Group 2 at stage I to receive BCD-131 at a dose of 1.7 µg/kg x CR, and 3

[2] The DSMC will include principal investigators (4 persons) and a medical expert assigned for this study.

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	patients will be randomized to the reference group to receive Mircera® (randomization in a 3:1 ratio)[3]. After all the patients in Group 2 and 3 patients in the reference group (enrolled simultaneously with the patients receiving BCD-131 at a dose of 1.7 µg/kg) have received 2 injections of either BCD-131 at a dose of 1.7 µg/kg x CR or the reference drug and completed a 2-week follow-up period after the second injection (i.e. 1.5 months (42 days) after the first injection or 14 days after the second injection), the investigators will consider a possibility of including the next 9 patients in Group 3 (BCD-131, 2.75 µg/kg x CR depending on the dose of the previous therapy). At stage I, the decision on a possibility of including the next group of patients to receive a higher dose (2.75 µg/kg x CR) will be taken in the same way as described for the previous dose level. The treatment of patients in Group 2 at stage I and in the reference group (the next 3 patients) will not be interrupted and continue according to the study protocol. The patients will go on receiving the relevant drugs at the same dose or, according to the DSMC decision, at a lower dose if the treatment with the same dose of BCD-131 does not benefit the patient for safety reasons. After the DSMC members have taken a decision about further dose escalation, 9 patients will be randomized to Group 3 at stage I to receive BCD-131 at a dose of 2.75 µg/kg x CR, and 3 patients will be randomized to the reference group to receive Mircera® (randomization in a 3:1 ratio)[4]. The terms and parameters of safety evaluation of BCD-131 at a dose of 2.75 µg/kg x CR in patients in Group 3 at stage I will be the same as those in Group 1 and Group 2 at stage I. **<u>Stage II</u>** In any of the above-mentioned situations, patients will be further enrolled in stage II of the study according to the conditions of the screening period and stratification described above for stage

[3] If the DSMC members have taken a decision about the risk of including patients in the next dose levels of BCD-131 (1.7 µg/kg and 2.75 µg/kg x CR) based on the safety data obtained in Group 1 at stage I, new patients will not be enrolled in groups to receive the next dose levels of BCD-131.

[4] If the DSMC members have taken a decision about the risk of including patients in the next dose level of BCD-131 (2.75 µg/kg x CR) based on the safety data obtained in Group 2 at stage I, new patients will not be enrolled in groups to receive the next dose levels of BCD-131.

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	I. The total number of patients in each group, approved by the DSMC for participation in stage II, should be 25 patients including those randomized to the relevant group at stage I of the study. At stage I, more patients will be enrolled in the reference group to achieve the total number of 25 patients, including those randomized to the relevant group at stage I of the study. If, based on the decision of the DSMC, all the three dose levels (1.05, 1.7, and 2.75 µg/kg x CR) of BCD-131 have acceptable safety profiles at stage I, more patients will be enrolled in each of these three groups and in the reference group at stage II to compare the efficacy and safety of the selected treatment regimen for 21 weeks. In this case, stage II of the study will include the following groups: **Planned study groups provided the DSMC has approved the further study of the three dose levels of BCD-131:** • **Group 1:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of BCD-131, 1.05 µg/kg x CR[5], depending on the dose of the previous therapy, once a month until Week 21. • **Group 2:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of BCD-131, 1.7 µg/kg x CR, depending on the dose of the previous therapy, once a month until Week 21. • **Group 3:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of BCD-131, 2.75 µg/kg x CR, depending on the dose of the previous therapy, once a month until Week 21. • **Group 4:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of Mircera® once a month until Week 21, at a dose depending on

[5] The dose calculations for BCD-131 and Mircera® are provided in Section 1.5.1 "Description and Justification of Administration Mode, Doses, Dosage Regimen and Treatment Course" of the Study Protocol.

Monthly doses of BCD-131 and Mircera® depend on a stable dose of recombinant EPO (epoetin alfa or epoetin beta, or darbepoetin alfa) received by the patient for at least 2 weeks before signing the Informed Consent and during the screening period.

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	that of the previously administered recombinant EPO in accordance with the SmPC for Mircera®[6]. If, based on the decision of the DSMC, the first two dose levels (1.05 and 1.7 µg/kg x CR) of BCD-131 have acceptable safety profiles at stage I, more patients will be enrolled only in Group 1 and Group 2 of the test drug and in the reference group at stage II to compare the efficacy and safety of the selected treatment regimen for 21 weeks. Patients who at stage I had received BCD-131 at a dose of 2.75 µg/kg x CR, which later was not approved by the DSMC for stage II, will further receive BCD-131 at a dose of 1.7 µg/kg x CR (i.e. the preceding dose level) until Week 21; their data will be used for additional safety evaluation. In this case, stage II of the study will include the following groups: **Planned study groups provided the DSMC has approved the further study of BCD-131, 1.05 and 1.7 µg/kg x CR:** • **Group 1:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of BCD-131, 1.05 µg/kg x CR[7], depending on the dose of the previous therapy, once a month until Week 21. • **Group 2:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of BCD-131, 1.7 µg/kg x CR, depending on the dose of the previous therapy, once a month until Week 21. • **Group 3:** Patients in this group (only 9 patients who have been randomized to this group at stage I and received BCD-131, 2.75 µg/kg x CR) will receive a subcutaneous injection of BCD-131, 1.7 µg/kg x CR, depending on the dose of the previous therapy, once a month until Week 21, for the purpose of additional safety evaluation. • **Group 4:** Patients in this group (25 patients including those randomized to this group at stage I)

[6] http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=24dc1990-f2f5-4991-996b-b4ef599ba2a6&t=

[7] The dose calculations for BCD-131 and Mircera® are provided in Section 1.5.1 "Description and Justification of Administration Mode, Doses, Dosage Regimen and Treatment Course" of the Study Protocol.

Monthly doses of BCD-131 and Mircera® depend on a stable dose of recombinant EPO (epoetin alfa or epoetin beta, or darbepoetin alfa) received by the patient for at least 2 weeks before signing the Informed Consent and during the screening period.

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	will receive a subcutaneous injection of Mircera® once a month until Week 21, at a dose depending on that of the previously administered recombinant EPO in accordance with the SmPC for Mircera®[8]. If, based on the decision of the DSMC, only the first dose level (1.05 µg/kg x CR) of BCD-131 has an acceptable safety profile at stage I, more patients will be enrolled only in Group 1 of the test drug and in the reference group at stage II to compare the efficacy and safety of the selected treatment regimen for 21 weeks. Patients who at stage I had received BCD-131 at a dose of 1.7 µg/kg x CR, which later was not approved by the DSMC for stage II, will receive BCD-131 at a dose of 1.05 µg/kg x CR (i.e. the preceding dose level) until Week 21; their data will be used for additional safety evaluation. In this case, stage II of the study will include the following groups: **Planned study groups provided the DSMC has approved the further study of BCD-131, 1.05 µg/kg x CR:** • **Group 1:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of BCD-131, 1.05 µg/kg x CR[9], depending on the dose of the previous therapy, once a month until Week 21. • **Group 2:** Patients in this group (only 9 patients who have been randomized to this group at stage I and received BCD-131, 1.7 µg/kg x CR) will receive a subcutaneous injection of BCD-131, 1.05 µg/kg x CR, depending on the dose of the previous therapy, once a month until Week 21, for the purpose of additional safety evaluation. • **Group 4:** Patients in this group (25 patients including those randomized to this group at stage I) will receive a subcutaneous injection of Mircera® once a month until Week 21, at a dose depending on

[8] http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=24dc1990-f2f5-4991-996b-b4ef599ba2a6&t=

[9] The dose calculations for BCD-131 and Mircera® are provided in Section 1.5.1 "Description and Justification of Administration Mode, Doses, Dosage Regimen and Treatment Course" of the Study Protocol.

Monthly doses of BCD-131 and Mircera® depend on a stable dose of recombinant EPO (epoetin alfa or epoetin beta, or darbepoetin alfa) received by the patient for at least 2 weeks before signing the Informed Consent and during the screening period.

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	that of the previously administered recombinant EPO in accordance with the SmPC for Mircera®[10]. **Study Periods** The study will include the following periods: 1. Screening period (up to 28 days from the moment of signing the Patient Information Sheet and the Informed Consent Form, inclusive); 2. Treatment period (Week 1 – Week 21, inclusive); 3. Follow-up (28 days from the last injection of the test/reference drug at Week 21 of the study).
Study Population	Adult dialysis patients with renal anemia due to the end-stage chronic renal failure (stage 5D CKD), aged 18 to 75 years (inclusive) on the day of signing the ICF, with the established efficacy of dialysis (dialysis dose (Kt/v) ≥1.2 for patients on hemodialysis and Kt/v ≥1.7 for patients on peritoneal dialysis)[11]. For dialysis patients, the need for the standard hemodialysis procedure should be at least 12 hours per week. Patients receiving recombinant EPO therapy (epoetin alfa or epoetin beta, or darbepoetin alfa) for at least 3 months before signing the Informed Consent, with the stable recombinant EPO dosing (epoetin alfa or epoetin beta, qw, biw, tiw, or darbepoetin alfa, qw or q2w) for at least 2 weeks before signing the Informed Consent and during the screening period, with the hemoglobin level within target values (100-120 g/L, inclusive) for at least 2 weeks before signing the Informed Consent and at screening, will be eligible for inclusion.
Planned Sample Size	Maximum number of patients: 100 patients
Inclusion Criteria	1. Signed ICF to participate in the study. 2. Men and women aged 18 to 75 years inclusive at the moment of signing the ICF. 3. Documented end-stage renal failure. 4. Need for dialysis for at least 3 months before signing the ICF.

[10] http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=24dc1990-f2f5-4991-996b-b4ef599ba2a6&t=
[11] Kt/V = -Ln (R - 0.008 x t) + (4 - 3.5 x R) x UF/W
where Ln - natural logarithm; R - post-dialysis to pre-dialysis blood urea nitrogen (BUN) (or urea) ratio; t - dialysis duration in h; UF - ultrafiltration volume in L; W - post-dialysis weight of the patient.

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	5. For dialysis patients, according to the investigator, the need for the standard hemodialysis procedure should be at least 12 hours per week. 6. Documented treatment with recombinant EPO (epoetin alfa, epoetin beta, or darbepoetin alfa) for at least 3 months before signing the ICF. 7. Documented stable dose of recombinant EPO (epoetin alfa or epoetin beta, qw, biw, tiw, or darbepoetin alfa, qw or q2w) for at least 2 weeks before signing the ICF and during the screening period. 8. Documented target hemoglobin level (100-120 g/L inclusive) for 2 weeks before signing the ICF and at screening. 9. Efficacy of dialysis established at screening (dialysis dose (Kt/v) ≥1.2 for patients on hemodialysis, and Kt/v ≥1.7 for patients on peritoneal dialysis)[12]. 10. Transferrin saturation ≥20%, ferritin level > 100 ng/mL at screening. 11. Willingness of patients and their sexual partners with preserved reproductive function to use reliable contraception starting from signing the ICF and up to 4 weeks after the final dose of the drug product given within the clinical study. This requirement does not apply to patients after surgical sterilization or ≥ 2 years post-menopausal. Reliable methods of contraception include one barrier method in combination with one of the following methods: spermicides, intrauterine device/oral contraceptives. 12. Patient's ability (in the investigator's opinion) to follow the Protocol procedures.
Exclusion Criteria:	1. Any other diagnosed forms of anemia, except for renal anemia, including anemia of chronic disease (C-reactive protein (CRP) level >20 mg/L at screening). 2. Proven diagnosis of lupus nephritis or CKD due to systemic vasculitis[13].

[12] Kt/V = -Ln (R - 0.008 x t) + (4 - 3.5 x R) x UF/W
where Ln - natural logarithm; R - post-dialysis to pre-dialysis blood urea nitrogen (BUN) (or urea) ratio; t - dialysis duration in h; UF - ultrafiltration volume in L; W - post-dialysis weight of the patient.

[13] A note of the absence of this pathology should be made by the investigator in the source documents.

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	3. Platelet count <100x10^9/L at screening. 4. Planned (i.e. there are data on a tentative date of surgery and/or availability of a suitable donor) kidney transplant surgery during the expected period of participation in the study. 5. History of allergies (anaphylactic shock or multiple drug allergy syndrome) as told by the patient, and hypersensitivity to darbepoetin alfa or any components of the study drugs, or iron(III)-hydroxide sucrose complex. 6. Vaccination within 8 weeks prior to signing the ICF (as told by the patient). 7. Diagnosed liver cirrhosis complicated with portal hypertension and/or splenomegaly and/or ascites. 8. HIV-infection, acute hepatitis B, C, syphilis[14]. 9. ALT, AST levels >3xULN at screening. 10. Decompensated heart disorders (chronic heart failure (CHF), NYHA Class IV). 11. Resistant hypertension[15]. 12. Unstable angina pectoris. 13. Proven diagnosis of hemoglobinopathies, myelodysplastic syndrome, malignant blood or lymphoid disorders, pure red cell aplasia. 14. Severe secondary hyperparathyroidism (intact parathyroid hormone (PTH)>1000 pg/mL at screening). 15. Documented episodes of gastrointestinal bleeding within 3 weeks prior to signing the ICF. 16. Documented episodes of thrombosis in past medical history (acute myocardial infarction, stroke, transient ischemic attacks, deep venous thrombosis, pulmonary embolism) within 6 months prior to signing the ICF.

[14] The patient with anti-HCV antibodies detected at screening can be included in the study if all of the following conditions are met: negative qualitative PCR results for HCV RNA (this test is performed only if anti-HCV antibodies have been detected); no increased transaminase and bilirubin concentrations shown by blood biochemistry tests; the medical infections specialist has provided a documented conclusion that the patient has no HCV/cured HCV; and the Sponsor has approved the enrollment of this particular patient.
HBsAg test is performed during the examination for hepatitis B. In case of positive results for HBsAg, the patient cannot be included in the study.
In case of a positive reaction for syphilis, the patient can be included in the study by the decision of the Sponsor if the Dermatologist/Venerologist has provided a documented conclusion that the patient has no syphilis/cured syphilis. Additional examination may be required to confirm the diagnosis (at the discretion of dermatologist).
[15] Resistant hypertension is defined as high blood pressure above the target range despite the concurrent use of three anti-hypertensive drugs of different classes. In case blood pressure can be controlled using four or more antihypertensive drugs, such hypertension is still considered to be resistant.

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	17. Seizure disorders, including a history of epilepsy. 18. Documented major surgery within 1 month prior to signing the ICF. 19. Documented blood transfusion within 3 months prior to signing the ICF. 20. Any acute infections, relapses of chronic infections or any other chronic diseases that are present on the day of signing the Informed Consent and can, as judged by the Investigator, negatively affect the patient's safety during the study treatment. 21. History of severe depression, suicidal thoughts or suicide attempts[16]. 22. Documented malignancies except for cured basal-cell carcinoma and/or cervical cancer *in situ*. 23. Known alcoholic or drug dependence or signs of present alcoholic/drug dependence that, in the investigator's opinion, can be contraindications for the treatment with the test/reference drug products or limit the treatment compliance. 24. Participation in other clinical studies within 90 calendar days prior to signing the Informed Consent. 25. Pregnancy and breastfeeding.
Study Therapy	BCD-131 will be administered to patients in 3 of 4 groups. Patients in Group 1 will receive BCD-131 at a dose of 1.05 µg/kg x CR, in Group 2 – 1.7 µg/kg x CR, in Group 3 – 2.75 µg/kg x CR. In all the BCD-131 groups, a conversion ratio will be additionally used to calculate a monthly dose depending on the previous dose of epoetin (alfa or beta) or darbepoetin alfa. The calculated doses of BCD-131, the frequency (once a month) and route of administration (subcutaneous) have been selected based on the data from non-clinical studies and a Phase I clinical study of BCD-131 as well as on their comparison with the data and recommendations for use available for other recombinant epoetins. The ease of administration and applicability in clinical practice have been taken into account as well. BCD-131 and Mircera® will be injected on Day 1 of Week 1, Day 1 of Week 5, Day 1 of Week 9, Day 1 of Week 13,

[16] This exclusion criterion can be confirmed or rejected on the basis of documents or as told by the patient.

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Day 1 of Week 17, Day 1 of Week 21, i.e. each patient will receive 6 injections of the test or reference drug.

It should be noted that during the discussion of this clinical study design with leading Russian experts having extensive practical experience in using erythropoietins in dialysis patients with CKD, this approach was found to be optimal in terms of patients' safety and prevention of potential adverse events.

The table below shows the starting doses of BCD-131 in Groups 1, 2, 3 and the dose of Mircera® in the Mircera® group depending on the type and dose of previous treatment.

Dose Level	Previous dose of epoetin	Previous dose of darbepoetin alfa	Mircera® dose	BCD-131 dose in Group 1 (1.05 µg/kg x CR), subcutaneously	BCD-131 dose in Group 2 (1.7 µg/kg x CR), subcutaneously	BCD-131 dose in Group 3 (2.75 µg/kg x CR), subcutaneously
No.	IU/week	µg/week	µg/month	µg/month	µg/month	µg/month
1	1000 - 2000	5 - 10	40	40	60	80
2	>2000 - 4000	> 10 - 20	75	60	100	160
3	> 4000 - 6000	> 20 - 30	120	100	160	260
4	> 6000 - 8000	> 30 - 40	150	120	200	340
5	> 8000 - 10000	> 40 - 50	200	160	280	440
6	> 10000 - 12000	> 50 - 60	250	200	340	560
7	> 12000 - 14000	> 60 - 70	300	260	420	680
8	> 14000 - 16000	> 70 - 80	350	300	480	800
9	> 16000	> 80	>350	>300	>480	>800

Dose Management:

Due to intra-patient variability, occasional individual hemoglobin values for a patient above and below the desired hemoglobin level may be observed. Hemoglobin variability should be addressed through dose management (adjustment) with consideration for the hemoglobin target range of 100 to 120 g/L, inclusive.

In this clinical study, 9 dose levels have been calculated for each of the BCD-131 and Mircera® groups depending on the dose/type of the previous treatment received by the participant. When situations described in the table below occur, dose

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adjustment is required (i.e. the dose of the drug product used should be increased or decreased by one level). For example, if the starting monthly dose of BCD-131 given to a patient in Group 1 (1.05 µg/kg x CR) was set as 100 µg/month (third dose level), then when the hemoglobin level increases from >125 to <130 g/L, it is necessary to reduce the dose of the drug product to the previous dose level i.e. to 60 µg/month (second dose level). Or, for example, when a patient in Group 2 (BCD-131, 1.7 µg/kg x CR) receives the drug product at a dose of 200 µg/month (fourth dose level) and two sequential blood tests show the variation in the hemoglobin level from ≥95 to <100 g/L, it is necessary to increase the product dose to the next dose level, i.e. the next injected dose should be 280 µg/month (fifth dose level).

If, according to the investigator, a situation requiring a different approach to dose adjustment of the test/reference drug occurs, this should be discussed with the Sponsor.

The dose adjustment of the test/reference drug is required, if one of the situations described in the table below occur:

Hemoglobin level in complete blood count (CBC), g/L	Change in hemoglobin level since the last CBC	Required measures
<75	Any change over time	Repeat the CBC. If hemoglobin level remains <75 g/L, it is recommended that the dose is increased to the next dose level.
75 to <95	Decreased level or without change	It is recommended that the dose is increased to the next dose level.
75 to <95	Increased level	Maintenance dose (no dose adjustment is required)
≥95 до <100 during two sequential complete blood counts	Decreased level or without change	It is recommended that the dose is increased to the next dose level.
≥100 to ≤120	Any change over time	Maintenance dose (no dose adjustment is required)
>120 to ≤125 during two sequential complete blood counts	Increased level or without change	Maintenance dose (no dose adjustment is required)
>125 to <130	Decreased level	Maintenance dose (no dose adjustment is required)
>125 to <130	Increased level or without change	It is recommended that the dose is decreased to the previous dose level
≥130	Any change over time	Repeat the CBC. If the hemoglobin of ≥130 g/L is confirmed, the dose should be temporarily withheld until the hemoglobin decreases to 115 g/L, at which point therapy should be reinitiated at one dose level lower than the previous one.

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	Any	Increase by >20 g/L from the baseline for 4 weeks (or by >10 g/L for 2 weeks)	Repeat the CBC. It is recommended that the dose is decreased to the previous dose level
	Any	Reduction by >20 g/L from the baseline for 4 weeks (or by >10 g/L for 2 weeks)	Repeat the CBC. It is recommended that the dose is increased to the next dose level.

Study Procedures	Patients will be given the injections of the test/reference drug during their visits to the study site. During the clinical study, dialysis sessions will be conducted as scheduled according to the recommendations approved by the treating physician. The efficacy of the drug products will be evaluated upon the completion of all the study periods based on the comparison of hemoglobin values obtained throughout the evaluation period vs. baseline (primary efficacy endpoint) and based on secondary endpoints. Secondary efficacy endpoints will include changes in the hemoglobin over time, a proportion of patients with the target hemoglobin maintained throughout the entire study, a proportion of patients who required dose adjustment or blood transfusion, and the mean hemoglobin throughout the entire study. Safety evaluation will be based on the frequency and severity of AEs and SAEs in the treatment groups, laboratory and instrumental findings, and the analysis of the vital signs. The investigators will monitor main hematology and biochemistry markers, ECG results, vital signs as well as the results of general examination of the patients. Safety parameters will be analyzed throughout the study. To evaluate the immunogenicity of the study drugs, patients will take blood tests for binding or neutralizing antibodies to BCD-131 or Mircera®, depending on the treatment group. To detect antibodies to pegylated darbepoetin / methoxy polyethylene glycol-epoetin beta and analyze changes in their production over time, blood sampling will be performed before the first injection at Visit 1/Day 1, then at Week 9 and Week 23, and when pure red cell aplasia (PRCA) is suspected[17].

[17] **Diagnostic criteria for pure red cell aplasia**
Main signs:
rHuEPO therapy for at least 3 weeks;
Hemoglobin reduction by at least 1 g/L/day without blood transfusions;
Reticulocyte count below $10x10^9$/L;
No significant reduction in WBC and platelets.
Additional signs:
Skin and/or systemic allergic reactions.
Supporting assessment:
Bone marrow aspiration shows normal cellularity and <5% erythroblasts with evidence of a maturation block;

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	A limited number of patients (not more than 15 patients in each group) will have additional blood samples collected to study pharmacokinetics (PK) (serum concentrations of the drug product) and pharmacodynamics (PD) (absolute reticulocyte count). Based on the investigator's decision, during the period of intensive blood sampling for PK analysis (after injection 1), patients in the PK/PD subset may be hospitalized to the study site (this hospitalization will not be reported as a SAE). Since patients included in the PK/PD subset will have to make multiple additional visits to the study site for blood sampling, this may cause certain inconveniences. Therefore, the study provides compensation to these patients.
Overall Duration of the Study	The expected duration of the study is 30 months, including the periods of enrollment (12 months), treatment and follow-up as well as data collection and statistical analysis of the results. Each subject is expected to participate in the study for 28 weeks maximum, including the screening (4 weeks), treatment and follow-up periods.
Efficacy Evaluation	**Primary endpoint:** • Change in the hemoglobin vs. baseline during the evaluation period. The baseline hemoglobin will be calculated as the arithmetic mean of hemoglobin values obtained at screening and at Visit 1. The final hemoglobin value during the evaluation period will be calculated as the arithmetic mean of hemoglobin values obtained at Week 21 and Week 23. **Secondary endpoints:** • Relative number of patients (%) with the target hemoglobin level (100-120 g/L, inclusive) during Weeks 1-23; • Relative number of patients (%) who required dose adjustment during Weeks 1-23; • Relative number of patients (%) who required blood transfusion during Weeks 1-23; • Mean hemoglobin level during Weeks 1-23. **Methods of efficacy assessment:** The efficacy analysis will be based on the comparison of hemoglobin values obtained throughout the evaluation period vs. baseline, a proportion of patients with the target hemoglobin, a

Serum assay shows the presence of anti-erythropoietin NAbs.

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	proportion of patients who required blood transfusion and dose adjustment, and the mean hemoglobin. To evaluate the efficacy of BCD-131 and Mircera®, patients will take CBC tests to determine hemoglobin levels. The first test for hemoglobin will be taken at screening. During the treatment period, the hemoglobin will be determined once every 2 weeks during the first 2 months of the study, and then every 4 weeks. The primary efficacy endpoint will be analyzed after the clinical study completion.
Safety Evaluation	**Safety endpoints:** • The proportion of patients who developed AEs/SAEs that were treatment-emergent in the opinion of the investigator; • The proportion of patients in each group who developed Grade 3-4 AEs (CTCAE v.4.03) that were treatment-emergent in the opinion of the investigator; • The proportion of patients in each group who discontinued the study due to AEs/SAEs. The safety endpoints will be analyzed after the completion of all periods of the study. **Methods of safety evaluation:** The safety assessment will include periodic evaluation of vital signs (blood pressure, pulse, body temperature), hematology (RBC, Hb, reticulocytes, platelets, WBC differential etc.) and biochemistry (glucose, total bilirubin, AST, ALT, ferritin, transferrin saturation etc.), ECG monitoring, AE/SAE reporting.
Immunogenicity Assessment	• The proportion of BAb- and NAb-positive patients. Blood sampling for immunogenicity assessment (BAbs and NAbs) will be performed in all the patients included in the study before the first injection and then at Week 9 and Week 23. Immunogenicity endpoints will be analyzed after the study completion.
PK and PD Assessment (for a limited number of patients, max n=60)	**1) PK/PD endpoints:** **PK endpoints:** ✓ $AUC_{0–672\ h}$ (area under the concentration vs. time curve from the moment of injection to 672 h [28 days]) and $AUC_{0-\infty}$ (to infinity) after the first injection of the test/reference drug,

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	✓ C_{max} (maximum serum concentration of the drug product) after the first injection of the test/reference drug, ✓ C_{min} (minimum serum concentration of the drug product) at Weeks 5, 9, 13, 17, 21, ✓ T_{max} (time to maximum serum concentration) after the first injection of the test/reference drug, ✓ $T_{½}$ (half-life) after the first injection of the test/reference drug, ✓ K_{el} (elimination rate constant) after the first injection of the test/reference drug, ✓ CL (total clearance) after the first injection of the test/reference drug. **PD endpoints:** ✓ $AUEC_{0\text{-}672\ h}$ (area under the effect vs. time curve from the moment of injection to 672 h [28 days]) based on the change in the absolute reticulocyte count after the first injection of BCD-131/Mircera®, ✓ AC-E_{max} (maximum absolute reticulocyte count after the first injection of BCD-131/Mircera®). The PK analysis of the test drug will be based on the serum concentration of BCD-131 (pegylated darbepoetin). The PD analysis of BCD-131 will be based on the absolute reticulocyte count. The PK/PD study will include a limited number of patients (max 60 patients, i.e. 15 patients per group). Additional blood samples will be collected in these patients for PK/PD study. Blood sampling points for PK assessment: • 2 h, 1 h and 5 min before injection 1 (Day 1 of Week 1), • 3, 6, 12, 24, 48, 72, 96, 168, 336, 504 h after injection 1, • 672 h after injection 1 (i.e. immediately before injection 2 at Week 5), • Before injections 3, 4, 5, 6 (Weeks 9, 13, 17, 21). Blood sampling points for PD assessment: • 5 min before injection 1 (Week 1), • 3, 6, 12, 24, 48, 72, 96, 168, 336, 504 h after injection 1, • 672 h after injection 1 (i.e. immediately before injection 2 at Week 5).

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	Based on the investigator's decision, during the period of intensive blood sampling for PK/PD analysis (after injection 1), patients in the PK/PD subset may be hospitalized to the study site (this hospitalization will not be reported as a SAE). The PK/PD endpoints will be analyzed after the completion of all periods of the study.
Statistical Analysis	**Calculation of sample size** The number of patients to be enrolled in the study was calculated using literature data on the therapeutic efficacy of Mircera® obtained from a multicenter, randomized, open-label clinical study of the maintenance treatment of anemia in dialysis patients with chronic kidney disease[18]. While the study was being planned, a hypothesis about the equivalent efficacy of the test and reference drugs (H_0: $\|\varepsilon\| \geq \delta$, H_1: $\|\varepsilon\| < \delta$, where ε is the true difference in the mean efficacy between the groups, δ is the equivalence margin of the efficacy of the test and reference drugs) was tested using the following values of errors: type I error: 5% (α=0.05), type II error: 20% (β=0.2), with the 80% power. The efficacy variable used to calculate the sample size was set as the change in the hemoglobin level throughout the treatment in patients participating in the above-mentioned Phase II study[19]. To calculate the sample size, the investigators estimated the sample mean value and standard deviation for the efficacy parameter using median values and quartiles given in the above-mentioned study. The estimate was based on the approach described in the article by X.Wan, W.Wang[20]. The calculated number of patients was 10 subjects per group. Taking into account the evaluation of the primary efficacy endpoint of the test drug with the dose selection for subsequent phases and high probability of patient's early withdrawal (due to the main disease), 25 patients will be included in each group to get more accurate and relevant efficacy data. Thus, the study will

[18] F.Locatelli, G.Villa, A.L.M. de Francisco, et al. Effect of a continuous erythropoietin receptor activator (C.E.R.A.) on stable haemoglobin in patients with CKD on dialysis: once monthly administration. Current medical research and opinion, 2007, Vol. 23, No., 2007, 969–979

[19] F.Locatelli, G.Villa, A.L.M. de Francisco, et al. Effect of a continuous erythropoietin receptor activator (C.E.R.A.) on stable haemoglobin in patients with CKD on dialysis: once monthly administration. Current medical research and opinion, 2007, Vol. 23, No., 2007, 969–979.

[20] X.Wan, W.Wang, J. Liu, T.Tong. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology, 2014.

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	include up to 100 patients (25 patients in each group of BCD-131, if all the three groups are formed, and 25 patients in the reference group). **Selection of populations for analysis** **Efficacy analysis** The per-protocol analysis will be used to assess the efficacy of treatment using the primary endpoint. This analysis will include all the patients who completed the treatment according to the Protocol. The mITT-analysis will be used to evaluate the efficacy of treatment using secondary endpoints. The mITT-analysis will include all the patients who were randomized to receive at least one dose of the study drugs and were not withdrawn at the beginning of the study due to serious violations of the Protocol rules and inclusion/exclusion criteria. **Safety analysis** The safety population will include all the patients who received at least one dose of the test/reference drug. **Immunogenicity analysis** The immunogenicity analysis will include all the patients who received at least one dose of the test/reference drugs and who have samples (suitable for analysis) taken before the first injection and at least at one of the subsequent visits. **PK/PD Analysis** The PK/PD analysis will include patients with no missed / lost / damaged blood samples as follows: • Samples taken before injection 1 (at least 1 blood sample); • Not more than 2 blood samples taken after injection 1 to 672 h, inclusive; • Not more than 2 blood samples taken at visits of Week 9, Week 13, Week 17, Week 21 (for PK analysis). **Methods of Statistical Analysis** The efficacy analysis for the primary endpoint will be performed by calculating the 95% confidence interval for the difference in the frequencies and by its comparison with the selected equivalence margin of 10 g/L.

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	Statistical methods for other variables will be selected based on the type and distribution of raw data. The following tests will be used to compare quantitative data with normal distribution: two-tailed Student's test, Welch's test, ANOVA. The non-normally distributed quantitative data will be analyzed using the Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test, and the Friedman test. The categorical data will be processed with frequency tables, contingency tables, exact Fisher's test, test for equality of frequencies, χ^2 Pearson's test, and Cochran-Mantel-Haenszel test. **Reporting:** Upon the completion of all the study periods, the final report will be prepared. It will contain the data on the efficacy and safety of BCD-131 obtained in this study.