CLINICAL STUDY PROTOCOL

Protocol Title:	**An Open-Label Single Ascending Dose Clinical Study of 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)**
Protocol Number::	BCD-131-1
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SYNOPSIS	
Study Code:	BCD-131-1
Study Title:	An Open-Label Single Ascending Dose Clinical Study of 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).
Study Product:	BCD-131 — pegylated darbepoetin (JSC BIOCAD, Russia), solution for injection
Reference Drug 1	Mircera® — methoxy polyethylene glycol-epoetin beta (F. Hoffmann-La Roche Ltd., Switzerland) solution for intravenous and subcutaneous injection
Reference Drug 2	Aranesp® — darbepoetin alfa (Amgen Europe B.V., Netherlands), solution for injections
Population:	Healthy male volunteers aged 18 to 45 years
Study Sponsor:	JSC BIOCAD, Russia. Postal address: Petrovo Dalnee, Krasnogorsky District, Moscow Region, Russian Federation, 143422. Tel.: +7(495) 992 66 28, fax: +7(495) 992 82 98. Legal address: 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, Saint Petersburg, Russian Federation, 198515
Study Aims and Objectives	**Study aim**: To evaluate the tolerability, safety, pharmacokinetics, pharmacodynamics and immunogenicity of single ascending doses of BCD-131 in healthy volunteers as compared to Mircera® and Aranesp®. **Study objectives (Stage I):** 1. Establish the frequency and severity of adverse events following the administration of single ascending doses of BCD-131 to healthy volunteers. 2. Establish key pharmacokinetic (PK) parameters ($AUC_{0\text{-}1176\ h}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, $T_{½}$, K_{el} and CL) of BCD-131 following the administration of single ascending doses of the drug product to healthy volunteers.

	3. Establish pharmacodynamic (PD) parameters ($AUEC_{0–1176\ h}$, $AC\text{-}E_{max}$) of BCD-131 based on the absolute reticulocyte count and Hb values in the blood of healthy volunteers following the administration of single ascending doses of BCD-131. 4. Study serum levels of binding antibodies (BAbs) in the blood of healthy volunteers following the subcutaneous administration of single ascending doses of BCD-131. 5. Establish main PK ($AUC_{0\text{-}1176\ h}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, T½, K_{el} and CL) and PD parameters ($AUEC_{0–1176\ h}$, $AC\text{-}E_{max}$ based on changes in the absolute reticulocyte count and Hb levels in the blood) as well as immunogenicity of therapeutic doses of Mircera® and Aranesp® given as subcutaneous injections to healthy volunteers. 6. Establish a safe dose of subcutaneous BCD-131 to be used at stage II of the study. **Study objectives (Stage II):** 1. Establish key pharmacokinetic parameters ($AUC_{0\text{-}1176\ h}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, $T_{½}$, K_{el} and CL) of BCD-131 given as a single subcutaneous or intravenous injection to healthy volunteers at a dose established at stage I of the study. 2. Establish key pharmacodynamic parameters ($AUEC_{0–1176\ h}$, $AC\text{-}E_{max}$ based on changes in the absolute reticulocyte count and Hb levels in the blood) of BCD-131 given as a single subcutaneous or intravenous injection to healthy volunteers at a dose established at stage I of the study. 3. Establish the frequency and severity of adverse events and evaluate the level of BAbs to BCD-131 given as a single subcutaneous or intravenous injection to healthy volunteers at a dose established at stage I of the study. 4. Establish subcutaneous and intravenous doses of BCD-131 to be used in a phase II clinical study.
Study Design:	**Stage I** Stage I of clinical study BCD-131-1 is an open-label, non-randomized clinical study of pharmacokinetics, pharmacodynamics, tolerability, safety and immunogenicity of the novel drug product given to healthy volunteers at ascending doses (Phase 1, a traditional "3+3" design). Also, at stage I the investigators will evaluate the PK and PD parameters of the closest analogues of BCD-131 (Mircera® and Aranesp®) given as subcutaneous injections at therapeutic doses. Volunteers (no more than 54 subjects at stage I) will be included in the study after they have signed an informed consent form, completed an examination at screening (no more than 14 days) and received the approval of the investigator confirming their eligibility for the study.

	Evaluation of pharmacokinetics, pharmacodynamics and safety of ascending doses of BCD-131 The evaluation of pharmacokinetics, safety and tolerability of BCD-131 will be conducted in 8 cohorts: 1. Cohort 01 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 0.05 µg/kg body weight. 2. Cohort 02 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 0.15 µg/kg body weight. 3. Cohort 03 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 0.40 µg/kg body weight. 4. Cohort 04 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 1.05 µg/kg body weight. 5. Cohort 05 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 1.70 µg/kg body weight. 6. Cohort 06 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 2.75 µg/kg body weight. 7. Cohort 07 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 4.45 µg/kg body weight. Volunteers will be included in the study in a consecutive order. First, three volunteers will be included in Cohort 01 to receive a single subcutaneous injection of BCD-131 at a calculated starting safe dose of 0.05 µg/kg. If during 14 days after the injection these volunteers do not develop any treatment-emergent Grade 3–4 adverse events, the next three volunteers will be included in the study (Cohort 02). The further inclusion algorithm is as follows: If during 14 days after the injection of BCD-131 the subjects do not develop any treatment-emergent Grade 3-4 AEs (DLT), the next cohort consisting of three volunteers will be included in the study to receive an escalated dose of BCD-131 (Cohort 03, Cohort 04, Cohort 05 etc.). If during 14 days after the injection of BCD-131 only one volunteer (of three) develops a treatment-emergent Grade 3-4 AE (DLT), three more healthy volunteers will be included in this cohort to receive BCD-131.

	If two subjects develop treatment-emergent Grade 3-4 AEs (DLT), the dose of BCD-131 which resulted in these events is considered to be the maximum tolerated dose (MTD). No further dose escalating is performed. Thus, the dose-limiting toxicity is assessed as close as possible to the time of drug administration during the first 14 days after the injection. However, follow-up of volunteers does not stop; it will continue up to Day 50 from the moment of injection and include the monitoring of volunteers' health as well as safety and PK parameters of BCD-131. **Evaluation of pharmacokinetics, pharmacodynamics and safety of subcutaneous therapeutic doses of Mircera® and Aranesp®** Simultaneously with the evaluation of pharmacokinetics, pharmacodynamics and safety of ascending doses of BCD-131, the investigators will evaluate the pharmacokinetics, pharmacodynamics and safety of subcutaneous therapeutic doses of Mircera® and Aranesp®. For this purpose, 12 more volunteers will be included in the study. After having been randomized in a 1:1 ratio, the volunteers will be assigned to 2 groups. Six volunteers in Group 1 will receive a single subcutaneous injection of Mircera® at a dose of 1.20 µg/kg (Day 1). Six volunteers in Group 2 will receive a single subcutaneous injection of Aranesp® at a dose of 0.45 µg/kg (Day 1). After the last volunteer enrolled in stage I of the study has completed all the procedures specified in the Study Protocol, an interim analysis of the data obtained will be performed. Based on the comparison of pharmacokinetics, pharmacodynamics and safety of different doses of the test drug and active comparators, the investigators will establish a dose of BCD-131 which ensures PD effects similar to those of the closest analogues (Mircera®, Aranesp®) given as subcutaneous injections at therapeutic doses. The established dose of BCD-131 will be used at stage II of the study.

	Subjects will be asked to stay at the study site for the first 24 h after the injection because multiple blood samples are to be collected over this period. Regardless of the group/cohort to which a volunteer has been assigned, s/he will be followed-up for 50 days during which 16 visits will be performed. **Stage II** Stage II of the study aims to further evaluate pharmacokinetics, pharmacodynamics and safety of subcutaneous and intravenous injections of BCD-131 at a dose which ensures PD effects similar to those of the closest analogues (Mircera®, Aranesp®) given as subcutaneous injections at therapeutic doses. For this purpose, 12 volunteers will be included in the study after they have signed an informed consent form, completed an examination at screening (no more than 14 days) and received the approval of the investigator confirming their eligibility for the study. After having been randomized in a 1:1 ratio, the volunteers will be assigned to 2 groups. • Six volunteers in Group 1 will receive a single intravenous injection of BCD-131 at a dose established at stage I of the study (Day 1). • Six volunteers in Group 2 will receive a single subcutaneous injection of BCD-131 at a dose established at stage I of the study (Day 1). Subjects will be asked to stay at the study site for the first 24 h after the injection because multiple blood samples are to be collected over this period. Regardless of the group/cohort to which a volunteer has been assigned, s/he will be followed-up for 50 days during which 16 visits will be performed.
Use of BCD-131 at Stage I	The test drug and reference drugs will be used in accordance with the study design: **Evaluation of pharmacokinetics, pharmacodynamics and safety of ascending doses of BCD-131**

	1. Cohort 01 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 0.05 µg/kg body weight. 2. Cohort 02 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 0.15 µg/kg body weight. 3. Cohort 03 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 0.40 µg/kg body weight. 4. Cohort 04 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 1.05 µg/kg body weight. 5. Cohort 05 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 1.70 µg/kg body weight. 6. Cohort 06 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 2.75 µg/kg body weight. 7. Cohort 07 will include no more than 6 volunteers who will receive a single subcutaneous injection of BCD-131 at a dose of 4.45 µg/kg body weight. **Evaluation of pharmacokinetics, pharmacodynamics and safety of subcutaneous therapeutic doses of Mircera® and Aranesp®** Group 1: Six volunteers will receive a single subcutaneous injection of Mircera® at a dose of 1.20 µg/kg. Group 2: Six volunteers will receive a single subcutaneous injection of Aranesp® at a dose of 0.45 µg/kg.
Use of BCD-131 at Stage II	BCD-131 will be used in accordance with the study design: Group 1: Six volunteers will receive a single intravenous injection of BCD-131 at a dose established at stage I of the study. Group 2: Six volunteers will receive a single subcutaneous injection of BCD-131 at a dose established at stage I of the study.
Time Points for Blood Sampling to Evaluate PK at Stage I of the Study	In the groups of volunteers receiving BCD-131 and Mircera®, blood sampling for the PK evaluation will be performed as follows: 1. PK1-1 — 5 min before the injection of BCD-131/Mircera® 2. PK2-1 — 30 ± 5 min after the injection of BCD-131/Mircera® 3. PK3-1 — 2 h ± 10 min after the injection of BCD-131/Mircera® 4. PK4-1 — 8 h ± 15 min after the injection of BCD-131/Mircera® 5. PK5-1 — 24 h ± 20 min after the injection of BCD-131/Mircera® 6. PK6-1 — 48 h ± 30 min after the injection of BCD-131/Mircera®

	7. PK7-1 — 72 h ± 30 min after the injection of BCD-131/Mircera® 8. PK8-1 — 96 h ± 60 min after the injection of BCD-131/Mircera® 9. PK9-1 — 120 h ± 60 min after the injection of BCD-131/Mircera® 10. PK10-1 — 168 h ± 60 min after the injection of BCD-131/Mircera® 11. PK11-1 — 216 h ± 120 min after the injection of BCD-131/Mircera® 12. PK12-1 — 288 h ± 120 min after the injection of BCD-131/Mircera® 13. PK13-1 — 336 h ± 120 min after the injection of BCD-131/Mircera® 14. PK14-1 — 504 h ± 120 min after the injection of BCD-131/Mircera® 15. PK15-1 — 672 h ± 120 min after the injection of BCD-131/Mircera® 16. PK16-1 — 840 h ± 120 min after the injection of BCD-131/Mircera® 17. PK17-1 — 1008 h ± 120 min after the injection of BCD-131/Mircera® 18. PK18-1 — 1176 h ± 120 min after the injection of BCD-131/Mircera® In the group of volunteers receiving Aranesp®, blood sampling for the PK evaluation will be performed as follows: 1. PK1-1 — 5 min before the injection of Aranesp® 2. PK2-1 — 30 ± 5 min after the injection of Aranesp® 3. PK3-1 — 2 h ± 10 min after the injection of Aranesp® 4. PK3-1 — 8 h ± 15 min after the injection of Aranesp® 5. PK5-1 — 16 h ± 20 min after the injection of Aranesp® 6. PK6-1 — 24 h ± 20 min after the injection of Aranesp® 7. PK7-1 — 36 h ± 30 min after the injection of Aranesp® 8. PK8-1 — 48 h ± 30 min after the injection of Aranesp® 9. PK9-1 — 72 h ± 30 min after the injection of Aranesp® 10. PK10-1 — 96 h ± 60 min after the injection of Aranesp® 11. PK11-1 — 120 h ± 60 min after the injection of Aranesp® 12. PK12-1 — 168 h ± 60 min after the injection of Aranesp® 13. PK13-1 — 216 h ± 120 min after the injection of Aranesp® 14. PK14-1 — 288 h ± 120 min after the injection of Aranesp® 15. PK15-1 — 336 h ± 120 min after the injection of Aranesp® 16. PK16-1 — 504 h ± 120 min after the injection of Aranesp® 17. PK17-1 — 672 h ± 120 min after the injection of Aranesp® 18. PK18-1 — 840 h ± 120 min after the injection of Aranesp® 19. PK19-1 — 1008 h ± 120 min after the injection of Aranesp® 20. PK20-1 — 1176 h ± 120 min after the injection of Aranesp®

Time Points for Blood Sampling to Evaluate PK at Stage II of the Study	1. PK1-2 — 5 min before the injection of BCD-131 2. PK2-2 — 15 ± 3 min after the injection of BCD-131 3. PK3-2 — 30 ± 5 min after the injection of BCD-131 4. PK4-2 — 60 ± 5 min after the injection of BCD-131 5. PK5-2 — 2 h ± 10 min after the injection of BCD-131 6. PK6-2 — 4 h ± 15 min after the injection of BCD-131 7. PK7-2 — 8 h ± 15 min after the injection of BCD-131 8. PK8-2 — 24 h ± 20 min after the injection of BCD-131 9. PK9-2 — 48 h ± 30 min after the injection of BCD-131 10. PK10-2 — 72 h ± 30 min after the injection of BCD-131 11. PK11-2 — 96 h ± 60 min after the injection of BCD-131 12. PK12-2 — 120 h ± 60 min after the injection of BCD-131 13. PK13-2 — 168 h ± 60 min after the injection of BCD-131 14. PK14-2 — 216 h ± 120 min after the injection of BCD-131 15. PK15-2 — 288 h ± 120 min after the injection of BCD-131 16. PK16-2 — 336 h ± 120 min after the injection of BCD-131 17. PK17-2 — 504 h ± 120 min after the injection of BCD-131 18. PK18-2 — 672 h ± 120 min after the injection of BCD-131 19. PK19-2 — 840 h ± 120 min after the injection of BCD-131 20. PK20-2 — 1008 h ± 120 min after the injection of BCD-131 21. PK21-2 — 1176 h ± 120 min after the injection of BCD-131
Planned Sample Size:	Up to 66 healthy volunteers
Inclusion Criteria:	1. Signing of the Informed Consent Form; 2. Male sex; 3. Age of 18 to 45 years, inclusive; 4. BMI within normal limits (18.5–24.9 kg/m^2); 5. Healthy patients, which is proved by their medical history, physical examination and laboratory findings: • No clinically significant abnormalities of circulatory, respiratory, nervous, hematopoietic, endocrine and digestive systems, liver and kidneys in the past medical history and at screening; • No history of cardiovascular disorders or thyroid disorders; • No history of hematologic disorders, including but not limited to any type of anemia, myelodysplastic syndrome, blood cancers, hemolytic syndrome, hemoglobinopathies, coagulopathies; • CBC results within normal limits, including: o Hemoglobin within 132–173 g/L; o Hematocrit (based on CBC results) within 39–49%; o Platelet count within 150–400*10^9/L; o Absolute reticulocyte count within 30.4–93.5 * 10^9/L; • Blood biochemistry and urinalysis results within normal limits;

	• Serum ferritin within 20–250 μg/L; • Serum endogenous erythropoietin within 4.3–29.0 MIU/mL; • Hemodynamic parameters within normal limits: systolic blood pressure within 100–139 mmHg; diastolic blood pressure within 60–90 mmHg; heart rate within 50–90 bpm; • No history of chronic infections (tuberculosis) or chronic inflammation; • No hepatitis B or C, HIV, or syphilis; • No acute infections within 4 weeks prior to inclusion in the study; • No psychiatric disorders and other conditions (including depression) that can interfere with the volunteer's ability to follow the study protocol; • Well-being (in the volunteer's opinion) within 30 days prior to inclusion in the study; 6. No history of or current (at baseline) alcohol or drug abuse; 7. Ability of the volunteer, in the investigator's opinion, to follow the study protocol procedures; 8. Willingness of volunteers and their sexual partners with preserved reproductive potential to use reliable contraception within 2 weeks before inclusion in the study and up to 7 weeks after the injection of the test product. This criterion is not applicable to subjects who underwent surgical sterilization. Reliable methods of contraception include one barrier method in combination with one of the following methods: spermicides, intrauterine device/oral contraceptives (for sexual partners). 9. Willingness of volunteers to avoid alcohol intake within 24 hours before and 8 days after each injection of the test drug;
Exclusion Criteria:	1. History of treatment with erythropoietins or any other ESAs; 2. Acute bleeding, blood/plasma donation or blood transfusion within 2 months before inclusion in the study; 3. History of chronic bleeding; 4. Standard laboratory and instrumental findings outside normal limits at screening; 5. History of allergies (anaphylactic shock or multiple drug allergy syndrome); 6. Known allergy or intolerance to any components of the investigational product; 7. Major surgery within 30 days prior to screening, or surgery being scheduled for any time during the study; 8. Impossibility to install a venous catheter for blood sampling (e.g. because of skin disorders at the sites of venipuncture); 9. Diseases or other conditions that can interfere with the pharmacokinetics of the investigational drug (e.g. chronic liver, kidney, blood, circulatory system, lung or neuroendocrine diseases, including diabetes mellitus and others);

	10. History of fever of 40 °C or more; 11. History of elevated hepatic transaminases (above 2.5xULN); 12. Episodes of thrombosis and/or thromboembolia in past medical history (myocardial infarction, stroke, transient ischemic attacks, deep vein thrombosis, pulmonary embolism within 6 months prior to inclusion in the study) as well as an increased risk of deep vein thrombosis; 13. History of epileptic attacks or seizures; 14. History or current (at screening) depression, suicidal thoughts/ attempts; 15. Regular oral or parenteral use of any medications including over-the-counter drugs, vitamins and nutritional additives within 2 weeks before a scheduled injection of the test drug; 16. Use of drugs, including OTC products, that significantly affect the hemodynamics, hepatic function, etc. (barbiturates, omeprazole, cimetidine, etc.) within 30 days before a scheduled injection of the test drug; 17. Vaccination within 4 weeks before a scheduled injection of the test drug; 18. Smoking more than 10 cigarettes per day; 19. Consumption of more than 10 portions of alcohol per week (one portion equals to 0.5 L of beer, 200 mL of wine or 50 mL of ethanol) or a history of alcohol, drug or medication abuse; 20. Participation in other clinical studies within 1 month before screening or simultaneous participation in another clinical study; 21. Previous participation in this study.
Overall Duration of the Study:	The expected duration of the study is 12 months, including the periods of enrollment, screening, 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 no more than 64 days, including the screening period (up to 2 weeks) and the active phase of the study (50 days).
Endpoints to Evaluate Single-Dose PK:	Primary: ✓ $AUC_{0–1176\ h}$ (area under the concentration vs. time curve from the moment of injection to 1176 h [Day 50 of follow-up]) and $AUC_{0-\infty}$ (to infinity). Secondary: ✓ C_{max} (maximum serum concentration), ✓ T_{max} (time to C_{max}), ✓ $T_{½}$ (half-life), ✓ K_{el} (elimination constant), ✓ CL (total clearance).
PD Endpoints	Primary:

<table>
<tr><td></td><td>
✓ $AUEC_{0\text{-}1176\ h}$ (total area under the effect vs. time curve from the moment of injection to 1176 h [Day 50 of follow-up]) based on the change in the absolute reticulocyte count after a single-dose injection of the drug product.
✓ AC-E_{max} (absolute maximum increase in the test parameter vs. baseline) based on the change in the absolute reticulocyte count in the blood after a single-dose injection of the drug product.

Secondary:

✓ $AUEC_{0\text{-}1176\ h}$ (total area under the effect vs. time curve from the moment of injection to 1176 h [Day 50 of follow-up]) based on the change in the Hb level in the blood after a single-dose injection of the drug product.
✓ AC-E_{max} (absolute maximum increase in the test parameter vs. baseline) based on the change in the Hb level in the blood after a single-dose injection of the drug product.
</td></tr>
<tr><td>Endpoint for Pain Assessment</td><td>✓ The average VAS score evaluating the pain during the injection.</td></tr>
<tr><td>Safety Endpoints:</td><td>✓ Total SAEs.
✓ Total AEs.
✓ Incidence of administration site reactions.
✓ Incidence of Grade 3-4 AEs and SAEs.
✓ Frequency of early withdrawals due to AEs and SAEs.</td></tr>
<tr><td>Immunogenicity Endpoints</td><td>✓ Incidence of BAbs to the drug product on Day 50 from the moment of a single-dose injection of the drug.</td></tr>
<tr><td>Statistical Analysis</td><td>
Sample size calculation

The sample size for the study was calculated based on the “3+3” design used in the study of doses and additional test parameters:

<table>
<tr><th>Cohort</th><th>Dose, µg/kg</th><th>Number of volunteers to be enrolled (obligatory)</th><th>Number of volunteers who can be enrolled if DLT signs develop</th></tr>
<tr><td>01</td><td>0.05</td><td>3</td><td>3</td></tr>
<tr><td>02</td><td>0.15</td><td>3</td><td>3</td></tr>
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</td></tr>
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03	0.40	3	3
04	1.05	3	3
05	1.70	3	3
06	2.75	3	3
07	4.45	3	3

To assess the PK and PD of the closest analogues of BCD-131, 6 more volunteers will be included in the study to receive Mircera® and 6 more volunteers will be enrolled to receive Aranesp®.

To assess the PK and PD of BCD-131 given as a subcutaneous or intravenous injection at a dose established at stage I of the study, 6 more volunteers will be included in the study to receive BCD-131 as an intravenous injection and 6 more volunteers will be enrolled to receive BCD-131 as a subcutaneous injection.

Methods of analysis

The data will be statistically processed with Statistica 10.0 software. The following tests will be used to compare data with normal distribution: two-tailed Student's test and ANOVA. The Mann-Whitney test and ANOVA will be used to compare non-normally distributed data. The regression analysis will be used for quantitative efficacy data. The categorical data will be processed using the Fisher's exact test, Yates-corrected Pearson's test χ^2 and Cochran-Mantel-Haenszel test.

PK analysis

The PK analysis will include data of all volunteers who have received one dose of BCD-131 or reference drugs. If a subject has had more than two PK serum samples missed / lost / spoilt and skipped blood sampling time points more than twice, his/her data will not be included in the PK analysis.

PD analysis

The PD analysis will include data of all volunteers who have received one dose of BCD-131 or reference drugs. If a subject has had more than two PK serum samples missed / lost / spoilt and skipped blood

	sampling time points more than twice, his/her data will not be included in the PD analysis. **Safety analysis** The safety analysis will include all patients who have received one dose of the test/reference drug. **Immunogenicity analysis** The immunogenicity analysis will include data of all volunteers who have received one dose of BCD-131 or reference drugs. If a subject has had serum samples taken on Day 1 and Day 50 missed / lost / spoilt, his/her data will not be included in the immunogenicity analysis.