Cover page

- Official study title: **An Open-label, Dose Escalation Study of the Pharmacokinetics, Pharmacodynamics, Tolerability and Safety of Single Subcutaneous Doses of BCD-089 in Healthy Volunteers**
- NCT number: **NCT03103438**
- Document date **June 1, 2016**

BIOCAD
Biotechnology Company

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CLINICAL STUDY PROTOCOL

Protocol title:	**An Open-label, Dose Escalation Study of the Pharmacokinetics, Pharmacodynamics, Tolerability and Safety of Single Subcutaneous Doses of BCD-089 in Healthy Volunteers**
Protocol identification number:	**BCD-089-1**
Drafted on:	June 1, 2016
Protocol amendment number:	Not applicable
Protocol amendment approval date:	Not applicable
Protocol version:	v. 1.0
Name and address of the clinical study sponsor (monitor):	JSC BIOCAD, Russia Registered Office: 34A Svyazi Street, Strelna, Petrodvortsovy District, St. Petersburg 198515, Russia. Mailing address: Petrovo-Dalnee, Krasnogorsk District, Moscow Region 143422 Phone: +7 (495) 992-66-28, Fax: +7 (495) 992-82-98
Names and positions of persons authorized by the sponsor to sign the protocol and protocol amendments:	Roman Alekseevich Ivanov, Vice President, Research and Development Address: 34-A, Ulitsa Svyazi, Strelna, Petrodvortsovy District, St. Petersburg 198515, Russia. e-mail: ivanov@biocad.ru Tel.: +7 (812) 380 49 33, ext. 950
Full name, position, address and telephone number of the sponsor's designated medical expert for this study:	Yulia Valentinovna Usacheva, Medical Expert, Category II Address: 34-A, Ulitsa Svyazi, Strelna, Petrodvortsovy District, St. Petersburg 198515, Russia. e-mail: usacheva@biocad.ru Tel.: +7 (812) 380 49 33

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SIGNATURE PAGE

to version 1.0 of June 1, 2016 of Protocol "An Open-label, Dose Escalation Study of the Pharmacokinetics, Pharmacodynamics, Tolerability and Safety of Single Subcutaneous Doses of BCD-089 in Healthy Volunteers"

I, the undersigned, agree with the following:

1. I have fully read the provisions of this Protocol, accept them, and undertake to conduct the study in accordance with this Protocol and in compliance with ICH GCP, National Standard of the RF GOST R 52379-2005 "Good Clinical Practice" and the requirements of state regulatory authorities.
2. I will not deviate from Protocol without a prior written permission from the Sponsor, approved by the Ministry of Health of the Russian Federation and local ethics committees, except when necessary to prevent any immediate danger to a study subject.
3. I have qualified staff, required equipment, and sufficient time to conduct the study in accordance with this Protocol.
4. I will take all the necessary measures to ensure that the staff members involved in the study are adequately familiar with this Protocol and will appropriately fulfill their responsibilities during the study.
5. I agree to audit and inspection procedures according to the rules set by the Sponsor and state regulatory organs.
6. I understand that the text of this Protocol and all other materials and study results are confidential and are the Sponsor's property. I undertake not to disclose them to third parties, except in cases provided for by the current legislation of the Russian Federation.

Principal Investigator:

_____
Signature

_____
Full name

_____
Date

Vice President, Research and Development, JSC
BIOCAD R.A. Ivanov:

_____
Signature

_____
Date

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUMC	The total area under the curve of the product of time by the drug concentration
BAb	Binding antibody
BCD-089	Anti-interleukin 6 receptor monoclonal antibody developed by JSC BIOCAD
BP	Blood pressure
CD	Cluster of differentiation
CDR	Hypervariable part of the immunoglobulin responsible for binding to epitopes (complementary determining regions)
CG	Control group
CHF	Chronic heart failure
Cmax	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose limiting toxicity
DMARDS	Disease-modifying antirheumatic drugs
DMARDS	Disease-modifying anti-rheumatic drugs
DMOBE	Dose with minimal observable biological effects
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
Fc-fragment	Fragment crystallizable region
GCP	Good clinical practice
GCs	Glucocorticoids

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GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
IAP	Inflammation Area Percentage
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IL-6	Interleukin 6
INN	International nonproprietary name
JSC	Joint-stock company
LDH	Lactate dehydrogenase
LLN	Lower limit of normal range
MG	Main group
MIBDs	Medical immunobiological drugs
MP	Medicinal product
MRSD	Minimum recommended starting dose
MTD	Maximum tolerated dose
Nab	Neutralizing antibody
NFκB	Nuclear factor kappa-B
NO	Nitrogen monoxide
NOAEL	No observed adverse events level
PD	Pharmacodynamics
PIL	Patient Information Leaflet
PK	Pharmacokinetics
RA	Rheumatoid arthritis
RAMS	Russian Academy of Medical Sciences
RANKL	Receptor activator of nuclear factor kappa-B ligand
RI	Research institute

SAE	Serious adverse event
SC	subcutaneous
SD	Standard deviation
sIL6R	Soluble interleukin-6 receptor
SOP	Standard operating procedure
t½	Half-life
TD	Test drug
Th	T-helpers
TNF-α	Tumor necrosis factor-alpha
TO	Thoracic organs
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organization

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Information about Investigators responsible for the clinical study conduction and the medical organizations where the clinical studies are to be conducted

No. п.п.	Name of the (clinical) study site	Address of the (clinical)study site	Telephone	Full name of the Principal Investigator	Position of the Principal Investigator
1.	Limited Liability Company BioEq	23-Zh. Krasnogvargeyskiy per., Saint Petersburg 197342 Ж	+7 (812) 913-04-23; +7 (931) 371-77-07	Polina Mikhailovna Khlyabova	Chief physician, Limited Liability Company BioEc

Other organizations involved in the study (clinical laboratories and other medical and/or technical services)

No. п.п.	Name and role in the study	Address	Full name of the person carrying out the study	Position of the person carrying out the study	Telephone
1.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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No. п.п.	Name and role in the study	Address	Full name of the person carrying out the study	Position of the person carrying out the study	Telephone
	[redacted]	[redacted]			

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SYNOPSIS	
Study ID:	BCD-089-1
Study Title:	An Open-label, Dose Escalation Study of the Pharmacokinetics, Pharmacodynamics, Tolerability and Safety of Single Subcutaneous Doses of BCD-089 in Healthy Volunteers
Investigational Product (test drug):	BCD-089 - [redacted]
Population:	Healthy male volunteers aged 18 to 45 years.
Study Sponsor:	JSC BIOCAD, Russia. Mailing address: Petrovo-Dalnee, Krasnogorsk District, Moscow Region, Russian Federation, 143422. Tel.: +7 (495) 992 66 28, Fax: +7 (495) 992 82 98 Legal address: 34-A, Ulitsa Svyazi, Strelna, Petrodvortsovy District, St. Petersburg 198515, Russia
Study goals and objectives	**Study goal:** to evaluate tolerability, safety, and major pharmacokinetic and pharmacodynamic parameters of BCD-089 following single subcutaneous administration in increasing doses to healthy volunteers. **Study Objectives** 1. To determine the safe dose range of BCD-089, which will subsequently be used in the phase II clinical study; 2. To determine the proportion of study participants in whom a single subcutaneous administration of BCD-089 was accompanied by the development of adverse events, including the proportion of volunteers with neutropenia of varying severity; 3. To determine the main pharmacokinetic parameters (AUC_{0-1680}, $AUC_{0-\infty}$, C_{max}, T_{max}, T½, K_{el} and CL) of BCD-089 after a single subcutaneous injection in increasing doses to healthy volunteers; 4. To determine the main pharmacodynamic parameters (C_{max}, T_{max}, C_{min}, T_{min}, AUC_{0-1680}) for C-reactive protein, IL-6 and soluble receptor IL-6; 5. To determine the proportion of volunteers, in whom binding and/or neutralizing antibodies to BCD-089 were determined following its single administration.
Study design:	Clinical study No. BCD-089-1 is a classic open-label, single-center, non-randomized cohort clinical study of the pharmacokinetics, pharmacodynamics, tolerability and safety of a novel drug in healthy

	volunteers at increasing doses (phase 1, 3+3 design, with the first cohort consisting of one volunteer ("sentinel patient") who will receive the product at a dose with an additional safety factor relative to the calculated minimum starting safe dose). Before being included in the study, healthy volunteers have to sign a written informed consent after having read it, after which they will undergo a 14-day screening examination to confirm compliance with the eligibility criteria for the study. No additional requirements regarding a certain diet or restriction of physical activity, both during the screening period and throughout the study, are specified in this protocol. Study No. BCD-089-1 includes seven cohorts: 1. Cohort 01 (sentinel patient) - 1 volunteer to whom a single subcutaneous injection of BCD-089 at a dose of 0.06 mg/kg will be administered. 2. Cohort 02 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.3 mg/kg will be administered. 3. Cohort 03 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.625 mg/kg will be administered. 4. Cohort 04 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.0 mg/kg will be administered. 5. Cohort 05 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.6 mg/kg will be administered. 6. Cohort 06 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.2 mg/kg will be administered. 7. Cohort 07 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.9 mg/kg will be administered. The inclusion of volunteers in the study is sequential. The first to participate in the study is one volunteer, representing the cohort "01" (sentinel patient), who is administered a single subcutaneous injection of BCD-089 0.06 mg/kg. The injection is performed subcutaneously in the left or right front surface of the thigh (at a central point on the line between the iliac crest and the upper border of the patella). In the absence of grade 3-4 adverse events related to the test product, developing within the first 7 days after the injection, three volunteers are included in cohort 02.

	Further, the volunteer inclusion algorithm corresponds to the following general principle: In the absence of any grade 3-4 AEs (DLT) associated with the test product within 7 days after the injection, the next cohort of three volunteers with dose escalation will be included in the study - Cohort 03 (cohort 04, cohort 05, cohort 06, cohort 07). If grade 3-4 AEs (DLT) associated with the test product were recorded in only one volunteer in a cohort of three volunteers, three more healthy volunteers will be additionally included in this cohort. With the development of grade 3-4 AEs (DLT) associated with the test product in two of six volunteers, the dose at which this event was recorded will be taken as the maximum tolerated dose, further dose escalation will be ceased. Thus, dose limiting toxicity will be assessed close to the time of administration, during the first seven days after the injection. However, it is not the end of the volunteers follow-up - monitoring of their condition, as well as blood sampling for the study of pharmacokinetics, pharmacodynamics, immunogenicity and safety, will be carried out up to 71 days from the moment of injection. A 14-day screening examination and 13 subsequent visits are planned to be conducted during the study. The duration of the active phase of the study (from the moment of the drug injection to the final visit) is 71 days. Due to the need for multiple blood sampling, the volunteer has to stay at the study site for the first day after the injection.
Test drug administration	BCD-089 is administered according to the developed design: 1. Cohort 01 (sentinel patient) - 1 volunteer to whom a single subcutaneous injection of BCD-089 at a dose of 0.06 mg/kg will be administered. 2. Cohort 02 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.3 mg/kg will be administered. 3. Cohort 03 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.625 mg/kg will be administered. 4. Cohort 04 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.0 mg/kg will be administered.

	5. Cohort 05 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.6 mg/kg will be administered. 6. Cohort 06 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.2 mg/kg will be administered. 7. Cohort 07 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.9 mg/kg will be administered.
Time points for PK blood sampling	[redacted] 16. [redacted]
Time points for blood sampling for CRP, IL-6 and soluble IL-6 receptor testing	[redacted] 16. [redacted]

Time points for blood sampling for membrane receptor occupancy assay for BCD-089	[redacted] 5. [redacted]
Planned sample size:	Up to 37 healthy volunteers.
Inclusion criteria:	1. Signed informed consent; 2. Male; 3. Age 18 - 45 years inclusive; 4. Body mass index (BMI) within normal limits (18.5 - 30.0 kg/m^2); 5. A verified diagnosis of "healthy", established according to the medical history, physical examination and laboratory data: • absence in the history and at the time of the screening examination of clinically obvious impaired function of the cardiovascular, respiratory, nervous, hematopoietic, endocrine, gastrointestinal systems, liver and kidneys; • absence of history of cardiovascular diseases; • complete blood count, blood chemistry, and urinalysis results are within reference ranges adopted at the study site; • hemodynamic parameters within normal limits: SBP - within 100 - 120 mm Hg., DBP - within 60 - 80 mm Hg. Art., heart rate - 50 - 90 bpm; • absence of chronic infections (tuberculosis) or history of chronic inflammatory diseases; • absence of laboratory markers of hepatitis B, C, HIV and syphilis; • absence of acute infectious diseases within 4 weeks before inclusion in the study; • absence of mental disorders and any other conditions that can affect the ability of the participant to follow the requirements of the protocol, including depression; • satisfactory well-being (in the opinion of the volunteer) within 30 days before signing of the informed consent form; 6. Absence of evidence of alcohol abuse or drug addiction at the time of inclusion in the study or in medical history, as well as negative results at the screening alcohol breath test, together with a negative result of the urine drug test; 7. The ability of the volunteer to follow the Protocol procedures, in the Investigator's opinion;

	8. The willingness of volunteers and their sexual partners of childbearing potential to use reliable methods of contraception, starting 2 weeks before inclusion in the study and throughout the study (day of injection and 70 days from the date of its administration). This requirement does not apply to participants who underwent surgical sterilization. Reliable methods of contraception involve the use of 1 barrier method in combination with one of the following: spermicides, intrauterine device/oral contraceptives for the sexual partner; 9. Willingness not to drink alcohol within 24 hours before the administration of the test product and for 8 days after.
Non-inclusion criteria:	1. A history of use of monoclonal antibody products against interleukin-6 or its receptor; 2. Allergy history (anaphylactic shock or multidrug allergy); 3. Known allergy or intolerance to monoclonal antibody drugs (murine, chimeric, humanized, or human) or any other components of the study drug. 4. Extensive surgery less than within 30 days prior to signing the informed consent; 5. Severe infections (including those that required hospitalization or parenteral antimicrobial/antimycotic/antiviral/antiprotozoal treatment) within 6 months before signing the ICF; 6. Systemic antimicrobial/antimycotic/antiviral/antiprotozoal treatments within 2 months before signing the ICF; 7. More than 4 episodes of respiratory infections within 6 months before signing the informed consent form; 8. Impossibility to insert a venous catheter for blood sampling (for example, due to skin diseases at venipuncture sites); 9. Diseases or other conditions that can affect the pharmacokinetics of the test product (e.g., chronic liver, kidney, blood, cardiovascular, bronchopulmonary and neuroendocrine systems disorders (including diabetes mellitus) etc.); 10. A history of body temperature increase above 40°C; 11. A history of episodes of elevated hepatic transaminases above 2.5 x ULN; 12. Epileptic seizures, a history of seizures; 13. Current depression or a history of depression, suicidal thoughts/attempts at the time of the screening examination or a history of such behavior; 14. Regular use of any oral or parenteral medications, including over-the-counter drugs, vitamins, and dietary supplements within less than 2 weeks before signing the informed consent; 15. Use of medications, including OTC drugs that have a pronounced effect on hemodynamics, liver function, etc. (barbiturates,

	omeprazole, cimetidine, etc.) within less than 30 days before signing the informed consent form; 16. Use of medicinal products that affect the immune status (cytokines and their inducers, glucocorticoid hormones, etc.) within less than 2 months prior to signing the informed consent form; 17. Vaccination within 4 weeks prior to signing of informed consent form; 18. Values of standard laboratory tests and investigations results that are beyond the reference ranges; 19. Smoking more than 10 cigarettes per day; 20. Consumption of more than 10 units of alcohol per week (1 unit of alcohol is equivalent to ½ liter of beer, 200 mL of wine or 50 mL of liquor) or a history of alcoholism, drug addiction or drug abuse; 21. Donation of 450 mL or more of blood or plasma within 2 months prior to signing of the informed consent form; 22. Participation in other clinical studies within less than 2 months before signing the informed consent form or simultaneous participation in other clinical studies; 23. Prior participation in this clinical study.
Total duration of the study:	The estimated duration of the study is 7 months, including volunteers recruitment (up to 2 months), period of administration of the study drugs and follow-up of study participants, data collection and statistical analysis of the results. The expected duration of participation of each subject in the study is up to 85 weeks, including the screening period (up to 2 weeks) and the active phase of the study (71 days).
Pharmacokinetic endpoints	Primary: ✓ AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity). Secondary: ✓ C_{max} (maximum serum concentration of anti-IL-6 receptor antibody), ✓ T_{max} (time to maximum concentration); ✓ $T_{½}$ (half-life), ✓ K_{el} (elimination rate constant), ✓ CL (total clearance).
Pharmacodynamic endpoints	**1. Determination of C-reactive protein concentration:** Primary:

	✓ AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity). Secondary: ✓ C_{min} (minimum detectable concentration in blood serum), ✓ T_{min} (time to minimum serum concentration). **2. Determination of IL-6 concentration:** Primary: ✓ AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity). Secondary: ✓ C_{max} (maximum concentration in serum), ✓ T_{max} (time to maximum serum concentration). **3. Determination of soluble IL-6 receptor concentration:** Primary: ✓ AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity). Secondary: ✓ C_{max} (maximum concentration in serum), ✓ T_{max} (time to maximum serum concentration). It will be additionally calculated within the study of pharmacodynamics based on the results of flow cytometry: ✓ Percentage of occupancy of membrane IL-6 receptors with BCD-089 2 hours after drug administration, 168, 336 and 504 hours after single injection[1]
Pain assessment endpoint	✓ The mean pain score during the injection on the visual analogue scale.
Safety endpoints:	✓ Proportion of subjects who developed SAEs in each cohort. ✓ Proportion of subjects who developed AEs in each cohort.

[1] Given parameter is not an endpoint in the study.

<table>
<tr><td></td><td>
✓ Proportion of subjects who developed local reactions in each cohort.
✓ Proportion of subjects who developed grade 3-4 AEs and SAE in each cohort.
✓ Proportion of subjects who developed any grade neutropenia in each cohort.
✓ Proportion of subjects who discontinued the study due to AEs and SAEs in each cohort.
</td></tr>
<tr><td>Immunogenicity endpoints</td><td>
✓ The proportion of volunteers in which binding and/or neutralizing antibodies to BCD-089 were detected on day 71 from the moment of a single subcutaneous injection.
</td></tr>
<tr><td>Statistical analysis</td><td>
Calculation of Sample Size

The calculation of the study sample size was based on the "3 + 3” design and dose levels used in the study.
<table>
<tr><th>Volunteers cohort</th><th>Dose, mg/kg</th><th>Number of mandatory included volunteers</th><th>Number of volunteers that can be included in case of DLT development</th></tr>
<tr><td>01</td><td>0.06</td><td>1</td><td>0</td></tr>
<tr><td>02</td><td>0.3</td><td>3</td><td>3</td></tr>
<tr><td>03</td><td>0.625</td><td>3</td><td>3</td></tr>
<tr><td>04</td><td>1.0</td><td>3</td><td>3</td></tr>
<tr><td>05</td><td>1.6</td><td>3</td><td>3</td></tr>
<tr><td>06</td><td>2.2</td><td>3</td><td>3</td></tr>
<tr><td>07</td><td>2.9</td><td>3</td><td>3</td></tr>
</table>
Analysis methods

The statistical analysis of the obtained data will be conducted using SAS 10.0 software and the R programming language for statistical data processing. Mann-Whitney, Wilcoxon, Kruskal-Wallis, and Friedman tests will be used to compare quantitative and scaled data. The categorical data will be processed using the Fisher’s exact test and the χ^2 Pearson test.

Safety analysis

Safety analysis will include all volunteers who received the test drug.

Pharmacokinetic analysis
</td></tr>
</table>

	Pharmacokinetics analysis will include data from volunteers who have received BCD-089 and have had no more than two missing/lost/damaged blood serum samples for pharmacokinetics and had no more than two consecutive missing/lost/damaged samples and for whom a serum sample obtained before the test drug administration is available for the analysis. **Pharmacodynamic analysis** Pharmacodynamics analysis will include data from volunteers who have received BCD-089 and have had no more than two missing/lost/damaged of whole blood and/or blood serum for pharmacodynamics studies, and for whom a serum sample obtained before the test drug administration is available for the analysis. **Immunogenicity analysis** Immunogenicity analysis will include data from volunteers who have received BCD-089 and have not had missing/lost/damaged serum samples taken on Days 1 and 71 of the study. **Report preparation** Preparation of the final study report will be performed after the end of the procedures for examination of the last participant.

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1. STUDY RATIONALE

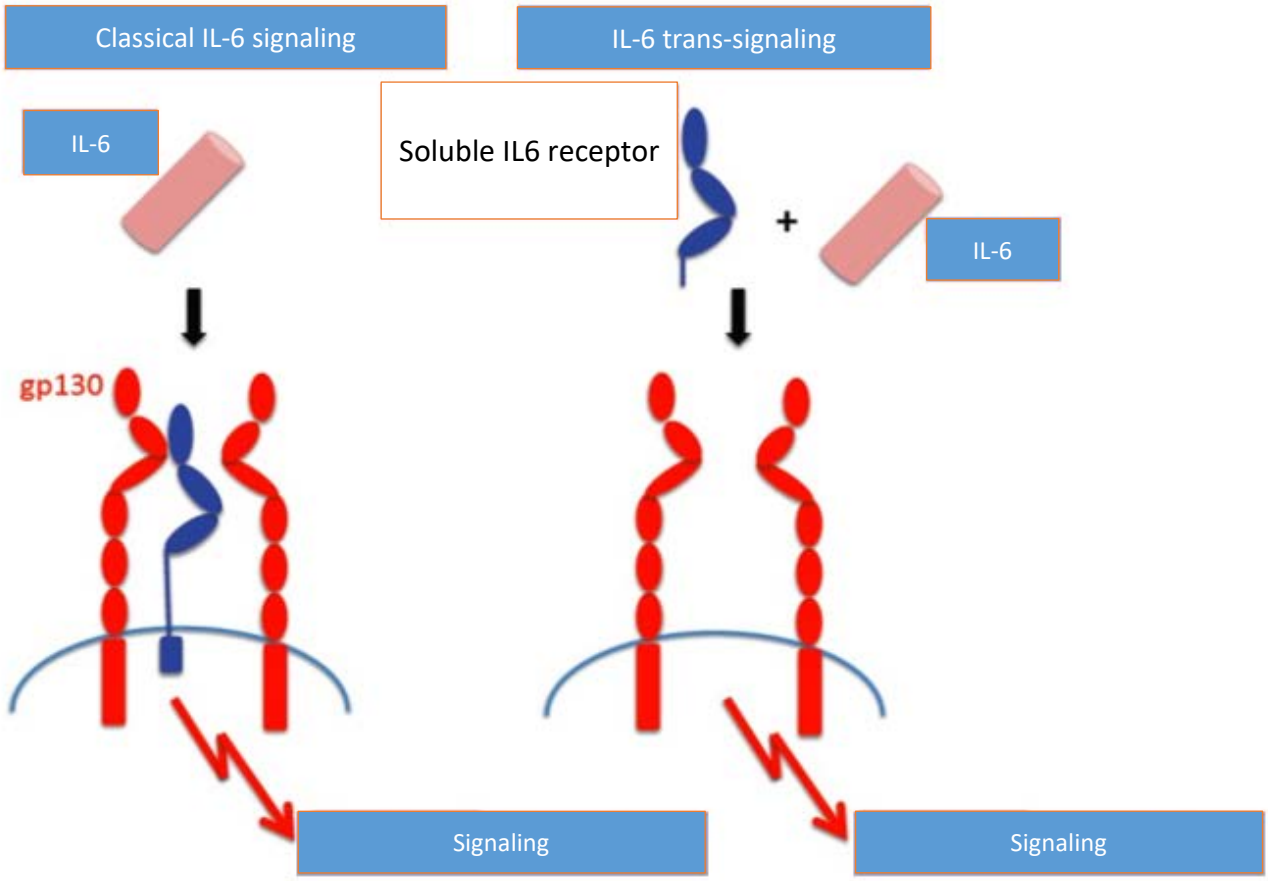
1.1. Introduction

Interleukin 6 (IL-6) is a pro-inflammatory cytokine with a wide biological activity, including an immunoregulatory component, affecting hematopoiesis, the development of inflammation, as well as carcinogenesis. Originally, IL-6 was identified as an antigen-non-specific factor for differentiation of B cells (Muragichi & all., 1981) (Yoshizaki & all., 1982) in mitogen/antigen-stimulated cultures of peripheral blood mononuclear cells. The cytokine is produced by various types of lymphoid and non-lymphoid cells such as T-lymphocytes, B-lymphocytes, monocytes, fibroblasts, keratinocytes, endothelial cells and some tumor cells (Kishimoto & all., 1995). IL-6 induces T-cell proliferation and differentiation of cytotoxic T-lymphocytes by increasing the expression of the IL-2 receptor (Noma & all., 1987) and the production of IL-2 itself (Garman & all., 1987). When evaluating the effect on the hematopoietic system, it was shown that IL-6 has similar activity to IL-3 in maintaining multipotent hematopoietic cells (Koike & all., 1988). The effect of IL-6 on the differentiation of macrophages (Nicola & all., 1983), megakaryocytes (Koike & all., 1990), and osteoclasts (Tamura, Udagava, & all., 1993) was also demonstrated. In the acute phase of inflammation, IL-6 induces the production of acute phase proteins, including C-reactive protein (Castell, Gomez-Lechon, & all., 1988). IL-6 is the main effector of joint inflammation and destructive changes associated with rheumatoid arthritis.

IL-6 triggers the transmission of the intracellular signal in two ways: by binding to the membrane IL-6 receptor (mIL-6R) and trans-signaling. The intracellular part of mIL-6R is not involved in signal transmission. For this, another protein is required—gp130 (IL-6R β chain, CD130), which is present in cells that do not express mIL-6R. Along with MIL-6R, there is a soluble form of the IL-6 receptor (sIL-6R), which, by forming a complex with IL-6, has the ability to bind to gp130 and induce the transmission of an activation signal without involvement of the membrane form (trans-signaling). While the classical effects of IL-6 are limited to the effect on mIL-6R-expressing cells (hepatocytes, monocytes, macrophages and some subpopulations of lymphocytes), trans-signaling allows IL-6 to activate cells lacking mIL-6R but expressing gp130, including synovial cells. This underlies a wide range of pathological effects of IL-6 in RA: fever,

increased concentrations of acute phase proteins, anemia, synthesis of autoantibodies, pannus formation and joint destruction, activation of Th17 cells, etc.

Figure 1. IL-6 classical signaling and IL-6 trans-signaling Classical IL-6 receptor signaling requires binding to mIL-6R and is limited to hepatocytes, some epithelial cells and some leukocytes. IL-6 trans-signaling requires sIL-6R and is possible on all cells of the body, since all cells express gp130 protein on their surface.



Classical IL-6 signaling via IL-6 membrane receptor

Membrane IL-6 and IL-6Rα receptors are found only on hepatocytes and some leukocytes (neutrophils, monocytes, T and B lymphocytes). Normally, IL-6Rα cannot transfer the signal inside the cell; to activate it, after binding to IL-6, it is necessary to form a complex with the homodimeric transducing protein gp130, which leads to the activation of the JAK1 kinase and transcription factor STAT3, which initiates differentiation and cell growth, prevents apoptosis and triggers the synthesis of Bcl2, Bcl-xL, TIMP proteins, LPS-binding protein, etc. The IL6-IL-6Rα-

gp130 signal leads to the activation of MAPK and ERK kinases activating the RAS proto-oncogen (GTPase, which mutates in various types of solid tumors).

Alternative signaling (trans-signaling) via soluble IL-6 receptor

The IL-6 receptor exists in soluble form in all bodily fluids (as a free receptor or as bound to IL-6). Such a receptor is capable of signaling in any cell that has gp130 on its surface (and such cells include the absolute majority of cells). IL-6 trans-signaling is apparently responsible for all pathological effects of this cytokine in inflammatory diseases of the connective tissue inflammatory bowel diseases and malignancies. sIL-6R plays a dual role. The formation of the IL6-sIL-6R complex not only protects IL-6 and extends its half-life, but also acts as an agonist that can directly activate cells through binding to gp130 (that is, unlike most soluble receptors, sIL-6R does not block, but rather promotes the IL-6 activity). This trans-signaling allows IL-6 to activate cells that have lost the alpha subunit of IL-6R, which normally would not respond to the action of this cytokine.

Blockade of both forms of the receptor will prevent the development of IL-6-associated pro-inflammatory cascade, including the prevention of activation of antigen-presenting cells, B and T lymphocytes, monocytes and macrophages, endothelial cells and fibroblasts (Kishimoto et al., 1989), as well as excess production of other pro-inflammatory cytokines, including IL-2 production by T cells. This cytokine stimulates T-cell proliferation and hematopoietic reactions (Kita et al., 1992). An imbalance between the pro- and anti-inflammatory effects of IL-6 has been demonstrated to cause various autoimmune diseases (e.g., rheumatoid arthritis), chronic inflammation and osteoporosis (Roodman et al., 1992), and psoriasis, while its excess production is associated with various forms of cancer. As a result, inhibition of the IL-6 action is an attractive target for research and treatment of these diseases.

Block of the soluble form of the IL-6 receptor, which is impossible when using antibodies to the ligand itself, allows to disrupt the alternative trans-signaling process.

Thus, the use of antagonistic anti-IL-6R antibodies will inhibit the main effects of this cytokine responsible for the development and maintenance of chronic inflammation in autoimmune diseases, and their use will allow:

- Impairing the differentiation of naive T-lymphocytes into Th17-lymphocytes—a population of autoimmune inflammatory cells that initiates the recruitment of immunocytes to inflammation sites.

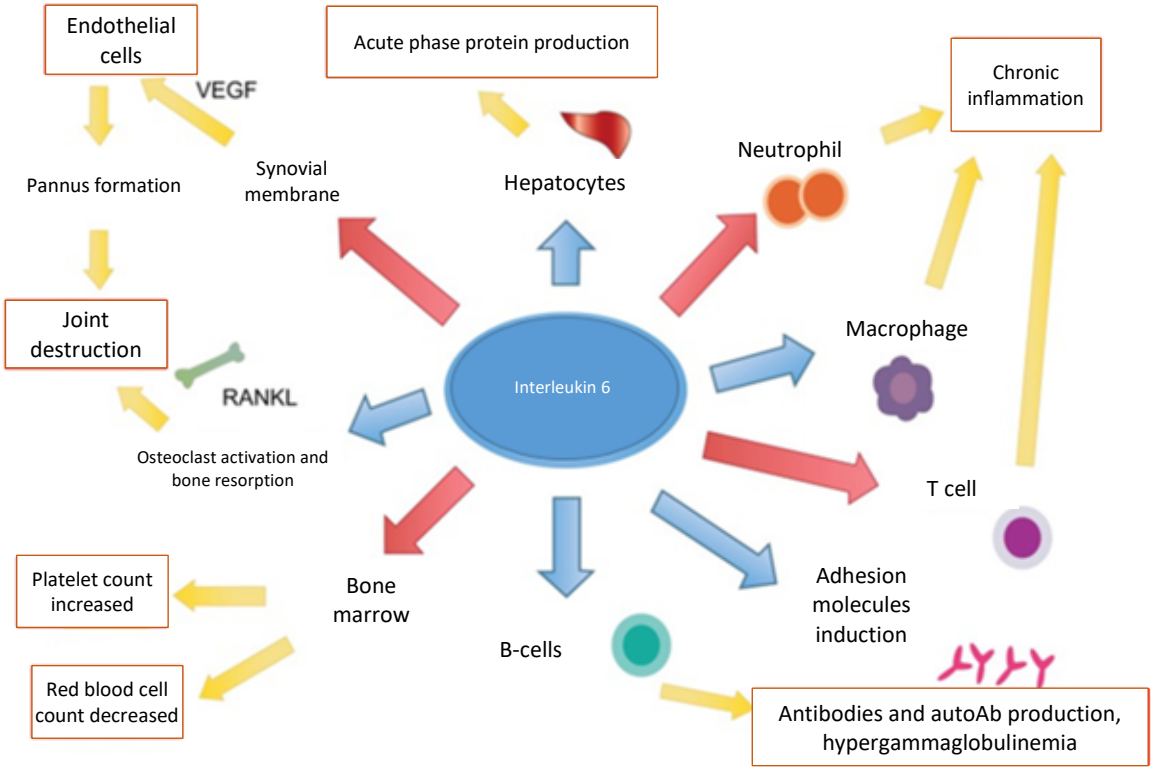
- Interfering with IL-6-dependent inhibition of regulatory T cell proliferation.
- Interfering with IL-6-promoted differentiation of CD4 lymphocytes into type 2 T-helpers, activation of mature T-lymphocytes and natural killers.
- Interfering with accumulation of autoreactive T cells by activating their apoptosis, as well as preventing the substitution of autoreactive T-cell binding to CD40 enabled by the IL-6/soluble IL-6 receptor complex.
- Interfering with the presentation of autoantigens by blocking IL-6-dependent inhibition by Na^{2+}/K^{+}-ATPase, which regulates the internalization of the antigen and its presentation to T cells by dendritic cells.
- Interfering with excessive activation, differentiation and proliferation of B-lymphocytes and antibody formation.
- Interfering with IL-6-dependent proliferation of osteoclasts and destruction of bone tissue.
- Neutralizing the oncogenic function of IL-6 due to its ability to activate intracellular signaling pathways aimed at stimulating proliferation and increasing the survival of most types of cells (via trans-signaling), and to normalize apoptosis.
- For malignancies characterized by elevated IL-6 levels (e.g. multiple myeloma, hepatocellular carcinoma, colorectal cancer, cardiac myxoma, Castleman disease) - preventing continuous IL-6-dependent autocrine stimulation.

Thus, an isolated blockade of signal transmission, carried out using an anti-IL-6R monoclonal antibody, is characterized by a wide range of anti-inflammatory and immunomodulatory effects, which determines the feasibility of further development and subsequent clinical use of this drug in patients with various autoimmune diseases, as well as determines the perspectives of studying its effects in the treatment of certain malignancies.

To date, the origin of rheumatoid arthritis remains unclear, however, it is known that a large number of cytokines, including IL-6, are detected in RA patients' serum and joint fluid. Since activated T cells are present in the synovial fluid of patients with rheumatoid arthritis, it has long been believed that the disease is Th1 type. However, this paradigm was revised after the presence of Th17 in the synovial fluid and the significant role of IL-17 in the development of RA were demonstrated (Chabaud & all., 1999). In this regard, it can be assumed that the role of IL-6 in the development of RA can be determined by two main functions, the recruitment of T cells and

induction of $CD4^+$ development towards Th17 (Naugler & Karin, 2007). A schematic representation of the mechanism of action of IL-6 is shown in Figure 2.

Figure 2. IL-6 as a link in inflammation, B-cell proliferation and hematopoiesis.



It has been shown that in inflammation, 'shedding' of soluble receptors from the surface of neutrophils leads, via trans-signaling, to the activation of endotheliocytes that do not express IL-6 receptors on their surfaces and are, therefore, not sensitive to the cytokine. Stimulation of endothelial cells by IL-6/sIL-6R complex causes the secretion of the cytokine MCP-1, leading to the migration of mononuclear cells to the site of inflammation. Thus, 'shedding' of the soluble IL-6 receptor determines damage, as measured by the number of neutrophils recruited to the inflammation site (DeLeo FR., 2007).

Therefore, shedding of IL-6 receptor and inhibition of their interaction between should have a pronounced effect on the development of inflammatory and destructive changes, which has been confirmed on an *in vivo* model of collagen-induced arthritis using cynomolgus monkeys (Mihara, Kotoh, & all, 2001) and demonstrated during the clinical use of tocilizumab.

The therapeutic mechanism of soluble IL-6 receptor blockade is shown in Figure 3.

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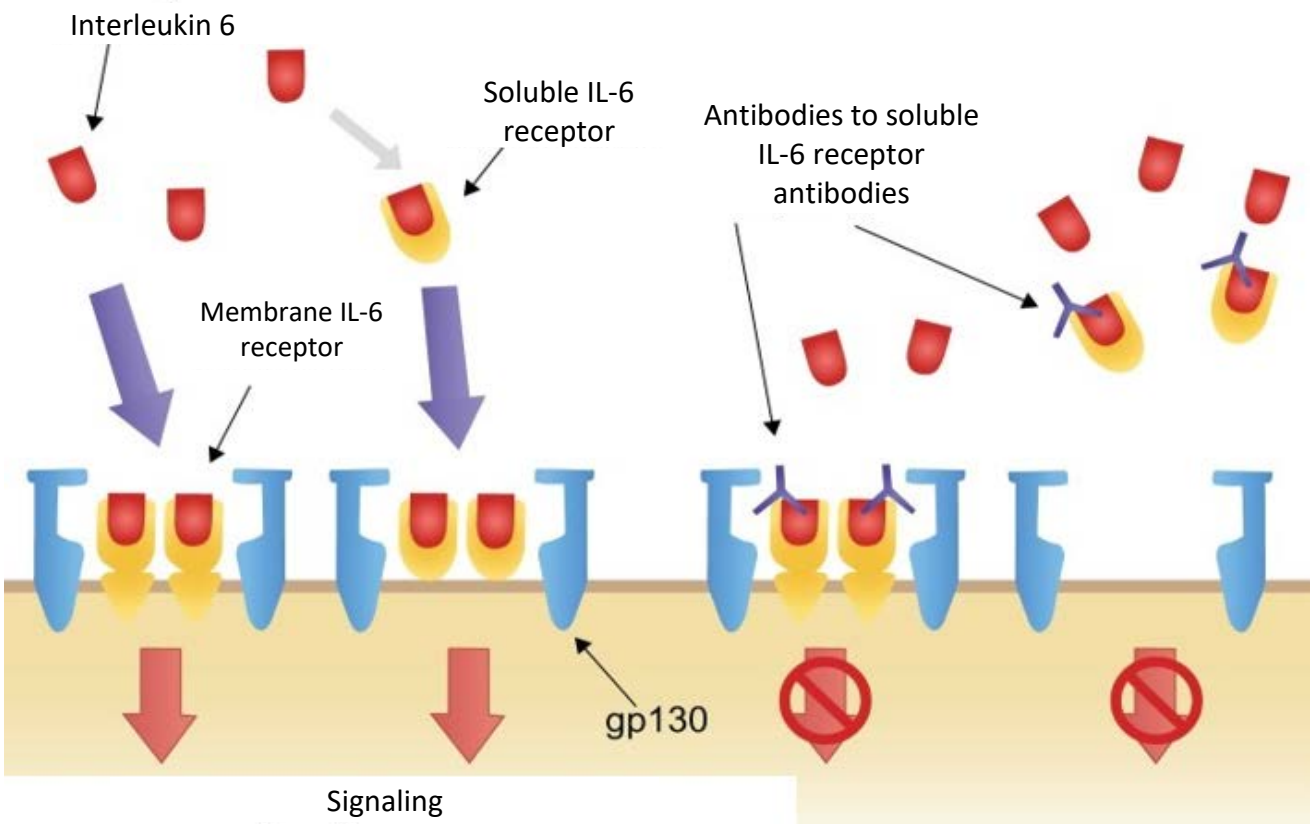
Figure 3. Therapeutic mechanism of soluble IL-6 receptor block



[redacted]

[redacted]

1.2. Name and description (characteristics) of the test drug

1.2.1. Test drug

Trade name: not applicable. Product code: BCD-089.

National nonproprietary name: Anti-interleukin-6 receptor monoclonal antibody

Pharmaceutical form: solution for injection.

Composition per 1 mL:

Active substance: [redacted]

Excipients:

[redacted]

Manufacturer: JSC BIOCAD, Russia

Shelf life: 2 years.

Storage and transportation conditions:

[redacted]

Packaging:

[redacted]

Labeling:

In accordance with Article 46 of Federal Law "On the Circulation of Medicinal Products" No. 61-ФЗ of April 12, 2010, the primary packaging of the test drug contains the following Russian text in easily readable font:

- name of the medicinal product: “BCD-089”,
- batch number,
- release date,
- expiry date,
- strength.

The secondary packaging contains the following information in Russian in easily readable font:

- name of the medicinal product: “BCD-089”,
- name of the medicinal product manufacturer: JSC BIOCAD, Russia,
- batch number,
- release date,
- expiry date,
- method of administration,
- strength;
- formulation,
- general classification for supply,
- storage conditions,
- cautionary information.

Primary and secondary packaging of the test drug will be additionally labeled with: “For clinical studies only”.

1.2.2 Diluent

The diluent in the study is needed to dilute the dosage form for administration to volunteers in the cohorts with less concentration

Composition of the diluent per 1 mL:

[redacted]

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[redacted] [redacted]

Manufacturer: JSC BIOCAD, Russia

Shelf life: 2 years.

Storage and transportation conditions:

[redacted]

Packaging:

[redacted]

Labeling:

In accordance with Article 46 of Federal Law "On the Circulation of Medicinal Products" No. 61-ФЗ of April 12, 2010, the primary packaging of the test drug contains the following Russian text in easily readable font:

- "Diluent",
- batch number,
- release date,
- expiry date,
- volume.

The secondary packaging contains the following information in Russian in easily readable font:

- name: "Diluent",
- manufacturer name: JSC BIOCAD, Russia,
- batch number,
- release date,
- expiry date,
- method of administration,
- volume,
- storage conditions,

- cautionary information.

Primary and secondary packaging of the test drug will be additionally labeled with: “For clinical studies only”.

Method of administration and dosing regimen:

In this study, the drug will be administered as a single-dose subcutaneously. The administered dose of BCD-089 depends on the cohort into which the volunteer was assigned:

1. Cohort 01 - 1 volunteer to whom a single subcutaneous injection of BCD-089 at a dose of 0.06 mg/kg will be administered.
2. Cohort 02 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.3 mg/kg will be administered.
3. Cohort 03 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.625 mg/kg will be administered.
4. Cohort 04 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.0 mg/kg will be administered.
5. Cohort 05 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.6 mg/kg will be administered.
6. Cohort 06 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.2 mg/kg will be administered.
7. Cohort 07 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.9 mg/kg will be administered.

Method of administration:

Dose calculation:

The dose is calculated in mg/kg of the volunteer's body weight. Based on the dose assigned according to the study design, the dose is calculated per 1 administration of the drug.

The total dose per 1 administration (mg) is equal to the weight of the volunteer (kg) multiplied by the dose specified for the cohort, which the volunteer is assigned to (mg/kg). A detailed table with the calculation of drug doses based on the volunteer body weight is provided to the Investigator.

Instructions for preparing the solutions for cohorts

Preparation of the solution for injection should be prepared using aseptic technique.

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[redacted]

[redacted]

1.3. Summary of potentially clinically relevant results of preclinical studies, as well as results of clinical studies that are relevant for this study

1.3.1. Non-clinical studies of the test drug

[redacted]

1.3.1.1. Summary of physicochemical studies

[redacted]

[redacted]

1.3.1.2. Preclinical studies in laboratory animals

1.3.1.2.1. A study of the potency of BCD-089 in a model of collagen-induced arthritis

[redacted]

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[redacted]

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1.3.1.2.2. BCD-089 pharmacokinetic study following a single-dose administration to monkeys

[redacted]

[redacted]

1.3.1.2.3. BCD-089 pharmacokinetic study following repeated-dose administration to monkeys

[redacted]

[redacted]

1.3.1.2.4. Study of BCD-089 immunogenicity following repeated-dose administration

[redacted]

[redacted]

1.3.1.2.5. Acute toxicity study of BCD-089

[redacted]

1.3.1.2.6. BCD-089 repeated-dose toxicity study

[redacted]

[redacted]

1.3.1.2.7. Evaluation of local tolerance of BCD-089 in a toxicity study with repeated-dose administration of the drug

[redacted]

[redacted]

1.3.1.2.8. BCD-089 cross-reactivity evaluation

[redacted]

1.3.1.2.9. Preclinical study of cytokine storm

[redacted]

1.3.2. Clinical studies of the test drug

Not performed.

1.4. Summary of known and potential risks and benefits for clinical trial subjects (risk/benefit ratio)

Benefit evaluation

BCD-089 is an innovative drug, which has never been used in humans. The first stage of BCD-089 clinical development will be to evaluate its effects in healthy volunteers, which means that participants in such a study will not derive subjective (personal) benefits from their participation in it, except for a detailed medical examination; however, data obtained after the completion of this study will have high scientific value and may help introduce into clinical practice a new highly effective product for the treatment of severe autoimmune disorders.

Risk evaluation

[redacted]

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[redacted]

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[redacted]

1.5. Description and justification of the study design, the method of administration of the test drug, dose, dosing regimen and the course of treatment

1.5.1. Description and justification of the study design

Clinical study No. BCD-089-1 is a classic open-label, single-center, non-randomized cohort clinical study of the pharmacokinetics, pharmacodynamics, tolerability and safety of a novel drug in healthy volunteers at increasing doses (phase 1, 3+3 design).

Study No. BCD-089-1 includes seven cohorts:

1. Cohort 01 - 1 volunteer to whom a single subcutaneous injection of BCD-089 at a dose of 0.06 mg/kg will be administered.
2. Cohort 02 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.3 mg/kg will be administered.
3. Cohort 03 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.625 mg/kg will be administered.
4. Cohort 04 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.0 mg/kg will be administered.
5. Cohort 05 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.6 mg/kg will be administered.
6. Cohort 06 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.2 mg/kg will be administered.
7. Cohort 07 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.9 mg/kg will be administered.

The inclusion of volunteers in the study is sequential. The first to participate in the study is one volunteer, representing the cohort “01”, who is administered a single subcutaneous injection of BCD-089 0.06 mg/kg. In the absence of grade 3-4 adverse events related to the test product, developing within the first 7 days after the injection, three volunteers are included in cohort 02, who will receive the estimated minimum single starting dose.

The doses for each cohort were calculated using a modified Fibonacci sequence.

According to the “3+3” principle, enrollment to the study is sequential. First, one volunteer is included in the first cohort. In the absence of grade 3-4 adverse events related to the test product,

developing within the first 7 days after the injection, three volunteers are included in cohort 02. Further, the volunteer inclusion algorithm corresponds to the following general principle:

a) In the absence of any grade 3-4 AEs (DLT) associated with the test product within 7 days after the injection, the next cohort of three volunteers with dose escalation is included in the study - cohort 02 (cohort 03, cohort 04, etc.).
b) If grade 3-4 AEs (DLT) associated with the test product are recorded in only one volunteer in a cohort of three volunteers, three more healthy volunteers are additionally included in this cohort.
c) With the development of grade 3-4 AEs (DLT) associated with the test product in two of six volunteers, the dose at which this event was recorded will be taken as the maximum tolerated dose, further dose escalation will be ceased.

Thus, dose limiting toxicity will be assessed close to the time of administration, during the first seven days after the injection. However, it is not the end of the volunteers follow-up - monitoring of their condition, as well as blood sampling for the study of pharmacokinetics, pharmacodynamics, and safety, will be carried out up to 71 days from the moment of injection - the selected duration of the study is sufficient for a full study of pharmacokinetics, pharmacodynamics and safety following a single-dose administration.

1.5.2. Justification of for the starting and maximum doses of BCD-089

1.5.2.1. Starting dose of BCD-089

According to the Guidelines for Conducting Preclinical Studies of Medicinal Products (part one)" (M.: FSBI "SCEEMP" of the Ministry of Health of Russia. - 2013, p. 854-864) for calculation of the maximum single starting dose (MSSD) for the first use of a novel drug in humans, it is necessary to determine the no-observed-adverse-effect level (NOAEL) in animals. The definition of NOAEL in the above guidelines says: "no-observed-adverse-effect level is the largest dose studied in animals, which does not cause a significant increase in **negative effects** compared to the control group. Negative effects that are biologically significant should be considered when determining NOAEL" (p. 855).

[redacted]

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[redacted]

[redacted]

1.5.2.2. Maximum BCD-089 dose in the study

[redacted]

[redacted]

1.5.3. Rationale for the route of administration and dosing frequency

[redacted]

1.6. Clinical study compliance with standard regulatory requirements

This clinical study will be conducted in compliance with this Protocol, which is fully compliant with the legislation of the Russian Federation, National Standard of the Russian Federation, GOST R 52379-2005 "Good Clinical Practice", as well as GCP standard.

1.7. Study population

Male healthy volunteers aged 18 to 45 years, inclusive who are eligible to participate in the study according to the Protocol eligibility criteria.

1.8. References

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2. STUDY GOALS AND OBJECTIVES

2.1. Study aims

To evaluate tolerability, safety, and major pharmacokinetic and pharmacodynamic parameters of BCD-089 following single subcutaneous administration in increasing doses to healthy volunteers.

2.2. Study Objectives

1. To determine the safe dose range of BCD-089, which will subsequently be used in the phase II clinical study;
2. To determine the proportion of study participants in whom a single subcutaneous administration of BCD-089 was accompanied by the development of adverse events, including the proportion of volunteers with neutropenia of varying severity;

3. To determine the main pharmacokinetic parameters (AUC_{0-1680}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{½}$, K_{el} and CL) of BCD-089 after a single subcutaneous injection in increasing doses to healthy volunteers;
4. To determine the main pharmacodynamic parameters (C_{max}, T_{max}, C_{min}, T_{min}, AUC_{0-1680}) for C-reactive protein, IL-6 and soluble receptor IL-6;
5. To determine the proportion of volunteers, in whom binding and/or neutralizing antibodies to BCD-089 were determined following its single administration.

3. HYPOTHESES TESTED

The study is based on the hypothesis that the maximum tolerated dose of BCD-089 with a single-dose subcutaneous injection to healthy volunteers is 2.9 mg/kg of body weight.

4. STUDY DESIGN

4.1 Primary and secondary parameters that will be assessed in the study

4.1.1. Pharmacokinetic endpoints

- AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity),
- C_{max} (maximum serum concentration of anti-IL-6 receptor antibody),
- T_{max} (time to maximum concentration);
- $T_{½}$ (half-life),
- K_{el} (elimination rate constant),
- CL (total clearance).

4.1.2. Pharmacodynamic endpoints

1. **C-reactive protein concentration determination:**

Primary:

- AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity).

Secondary:

- C_{min} (minimum detectable concentration in blood serum),
- T_{min} (time to minimum serum concentration).

2. **Determination of IL-6 concentration, soluble IL-6 receptor concentration:**

Primary:

- AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity).

Secondary:

- C_{max} (maximum concentration in serum),
- T_{max} (time to maximum serum concentration).

Additionally, the percentage of occupancy of membrane IL-6 receptors with BCD-089 2 hours after drug administration, 168, 336 and 504 hours after single injection will be determined in the study (however, it is not specified in the mandatory analyzed endpoints as it is a pilot study).

4.1.3. Subcutaneous injection-associated pain assessment endpoint

- The mean pain score during the injection on the visual analogue scale.

4.1.4. Safety endpoints:

- Proportion of subjects who developed SAEs in each cohort.
- Proportion of subjects who developed AEs in each cohort.
- Proportion of subjects who developed local reactions in each cohort.
- Proportion of subjects who developed grade 3-4 AEs in each cohort.
- Proportion of subjects who developed any grade neutropenia in each cohort.
- Proportion of subjects who discontinued the study due to AEs and SAEs in each cohort.

4.1.5. Immunogenicity endpoint

- The frequency of development of binding and/or neutralizing antibodies to BCD-089 on Day 71 from the moment of a single-dose subcutaneous injection.

4.2 Design

Clinical study No. BCD-089-1 is a classic open-label, single-center, non-randomized cohort clinical study of the pharmacokinetics, pharmacodynamics, tolerability and safety of a novel drug in healthy volunteers at increasing doses (phase 1, 3+3 design).

Before being included in the study, healthy volunteers have to sign a written informed consent after having read it, after which they will undergo a 14-day screening examination to confirm compliance with the eligibility criteria for the study. No additional requirements regarding a certain diet or restriction of physical activity, both during the screening period and throughout the study, are specified in this protocol.

Study No. BCD-089-1 includes seven cohorts:

1. Cohort 01 - 1 volunteer to whom a single subcutaneous injection of BCD-089 at a dose of 0.06 mg/kg will be administered.
2. Cohort 02 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.3 mg/kg will be administered.
3. Cohort 03 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.625 mg/kg will be administered.

4. Cohort 04 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.0 mg/kg will be administered.

5. Cohort 05 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.6 mg/kg will be administered.

6. Cohort 06 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.2 mg/kg will be administered.

7. Cohort 07 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.9 mg/kg will be administered.

***Note.** If a volunteer is administered 1 mL of the solution and, therefore, it is necessary to perform two injections to administer the calculated dose, it is preferable to administer the drug to the same anatomical region, provided that the site of the subsequent injection is no closer than 5 cm from the previous one. The duration of administering several injections should not exceed 10 minutes; calculation of time for PK sampling starts from the "last" drug injection.

The inclusion of volunteers in the study is sequential. The first to participate in the study is one volunteer, representing the cohort "01", who was administered a single subcutaneous injection of BCD-089 at a dose calculated with an additional safety factor relative to the safe starting dose - 0.06 mg/kg. In the absence of grade 3-4 adverse events related to the test product, developing within the first 7 days after the injection, three volunteers are included in cohort 02. Further, the volunteer inclusion algorithm corresponds to the following general principle:

In the absence of any grade 3-4 AEs (DLT) associated with the test product within 7 days after the injection, the next cohort of three volunteers with dose escalation is included in the study - cohort 02 (cohort 03, cohort 04, etc.).

If grade 3-4 AEs (DLT) associated with the test product are recorded in only one volunteer in a cohort of three volunteers, three more healthy volunteers are additionally included in this cohort.

With the development of grade 3-4 AEs (DLT) associated with the test product in two of six volunteers, the dose at which this event was recorded will be taken as the maximum tolerated dose, further dose escalation will be ceased.

Thus, dose limiting toxicity will be assessed close to the time of administration, during the first seven days after the injection. However, it is not the end of the volunteers follow-up -

monitoring of their condition, as well as blood sampling for the study of pharmacokinetics, pharmacodynamics, and safety, will be carried out up to 71 days from the moment of injection.

A 14-day screening examination and 13 subsequent visits are planned to be conducted during the study. The duration of the active phase of the study (from the moment of the drug injection to the final visit) is 71 days.

The volunteer will need to be in a hospital for the entire duration of the first visit procedures (during which the test drug will be administered), since at this visit multiple blood sampling for PK studies will be performed. The volunteer will be able to leave the study site 24 hours after the administration of the test drug, provided he/she feels well and all prescribed blood sampling is completed. Starting from the "Day 3" visit, the volunteer must come to the study site approximately 1 hour before the PK blood sampling.

Due to the need for multiple blood sampling, the volunteer has to stay at the study site for the first day after the injection.

Safety and tolerability assessment

Safety and tolerability will be assessed by monitoring vital signs (blood pressure, heart rate, and body temperature), conducting periodic physical examinations, assessing the frequency and severity of local reactions, and evaluating the results of complete blood count and blood biochemistry tests, urinalysis, and electrocardiography. These parameters will be assessed over a period of 71 days after a single-dose administration of the test drug. Additionally, information about the tenderness of subcutaneous injection, evaluated by a volunteer using a 10-point visual analog scale, will be analyzed.

Pharmacokinetic assessment

Pharmacokinetic assessment will be carried out based on data on the BCD-089 concentration in the serum of healthy volunteers. Volunteers included in the study arrive at the study site on the morning of the drug administration day. A venous catheter is installed immediately before the first blood sampling (the time from the catheter placement to the first blood sampling from it should not exceed one hour). Since multiple blood sampling is carried out only during the first day after the test drug administration, the time of placement a venous catheter will be 24 hours, after which the blood is taken by venipuncture. Detailed description of blood sampling points is presented in Table 3 below.

Table 3. Detailed description of blood sampling for PK assessment.

Visit	Sample labeling number	Blood sampling time	Acceptable window for blood sampling	Blood volume (for 2 aliquots)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Pharmacodynamics and immunogenicity assessment

Pharmacodynamics assessment will be carried out based on data on the concentrations of C-reactive protein, soluble IL-6 receptor, human IL-6 in the serum of healthy volunteers.

Table 4. Detailed description of blood sampling for CRP, sIL-6R, IL-6 testing

Visit	Sample labeling number	Blood sampling time	Acceptable window for blood sampling	Blood volume (for 3 types of analyzed substances)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Visit	Sample labeling number	Blood sampling time	Acceptable window for blood sampling	Blood volume (for 3 types of analyzed substances)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Visit	Sample labeling number	Blood sampling time	Acceptable window for blood sampling	Blood volume (for 3 types of analyzed substances)
	[redacted]			

Additionally, the percentage of occupancy of IL-6 membrane receptors with BCD-089 will be determined. Detailed description of blood sampling points is presented in Table 5 below.

Table 5. Detailed description of blood sampling for IL-6 receptor occupancy assay

Visit	Sample labeling number	Blood sampling time	Acceptable window for blood sampling	Blood volume
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6. Detailed description of blood sampling for immunogenicity assessment.

Visit	Sample labeling number	Blood sampling time	Acceptable window for blood sampling	Blood volume (for 3 aliquots)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Reporting:

The study report will be prepared after receiving data on the results of follow-up of the last volunteer included in the study.

Figure 7. Dose escalation scheme (starting from the cohort "02").

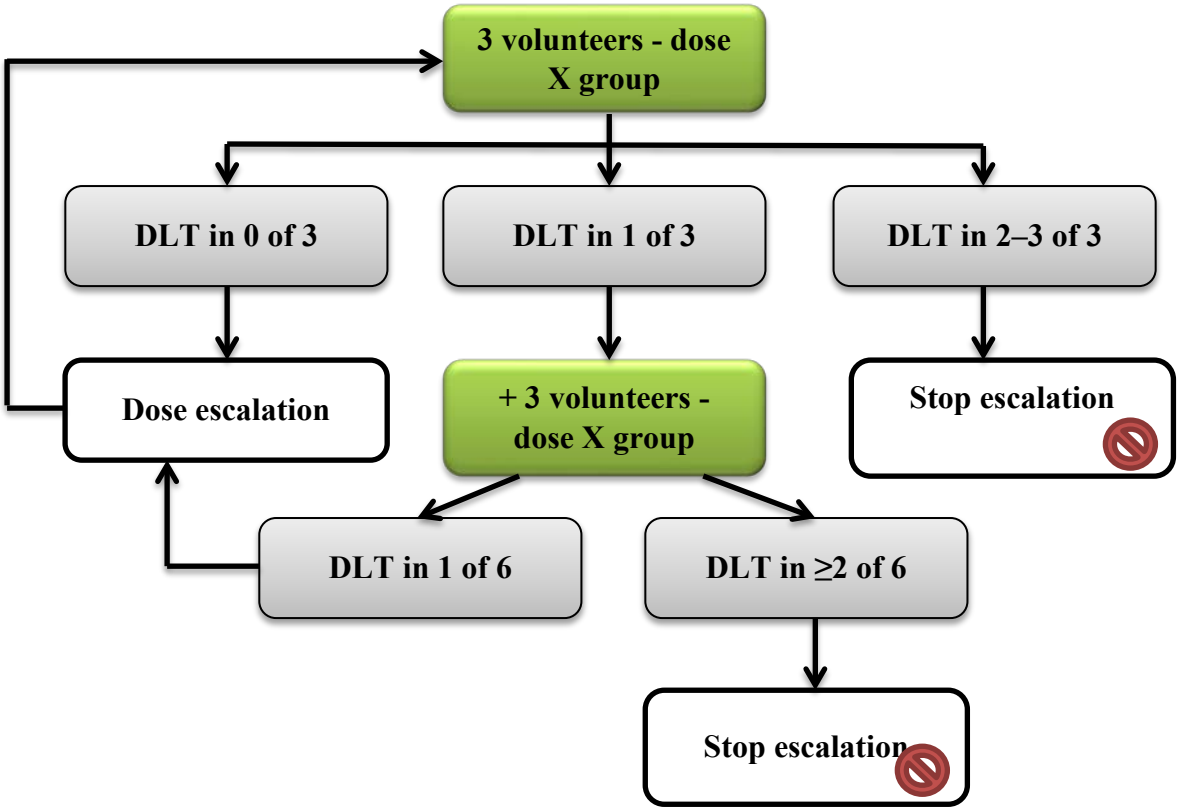

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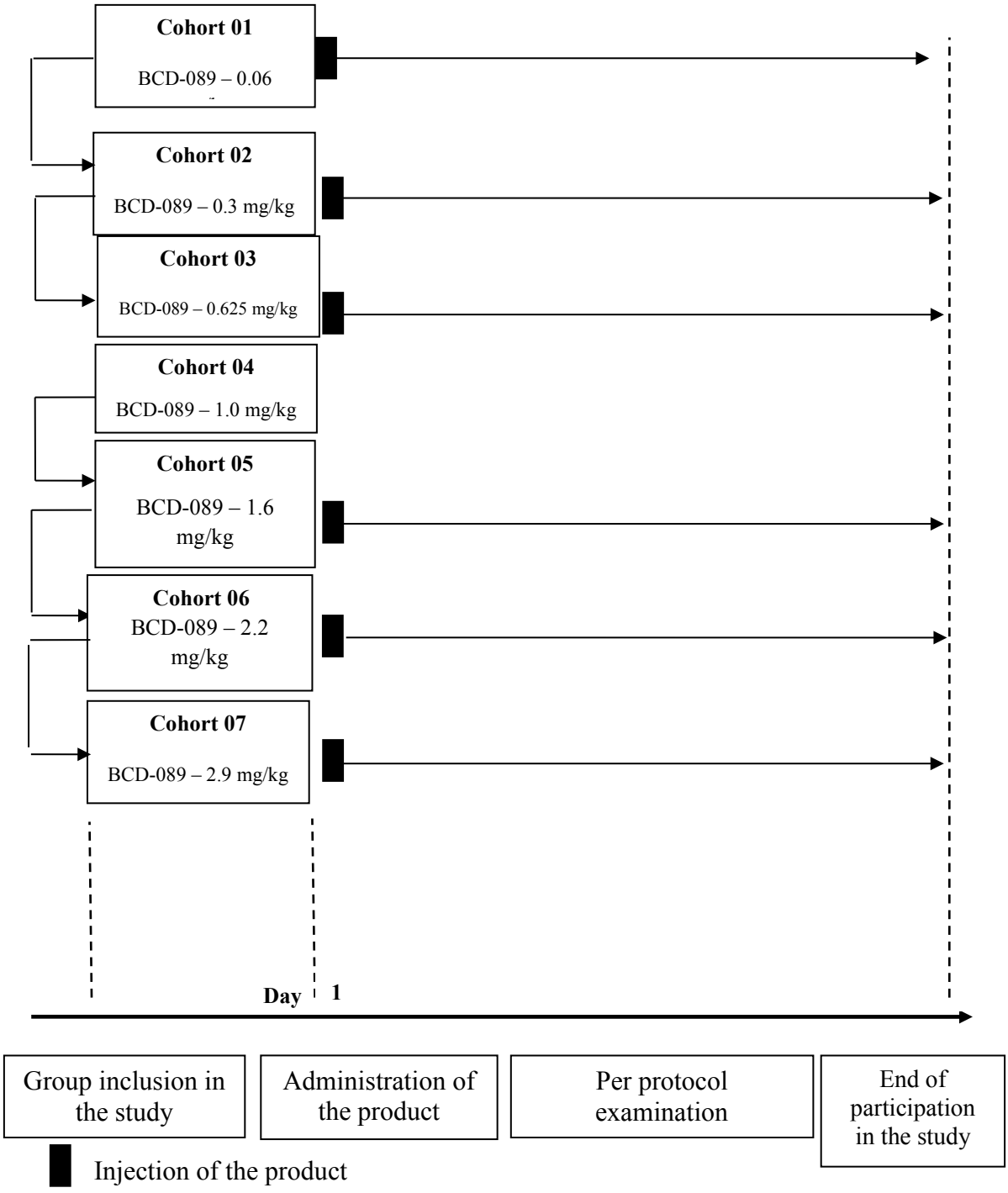
Figure 8. Study flowchart



4.3. Description of measures intended to minimize/exclude bias

4.3.1. The assignment of serial numbers to study sites

One study site is planned to be involved, and its number will consist of any two digits.

4.3.2. Assignment of a screening number

[redacted]

4.3.3. The inclusion of volunteers in the study, assignment of study numbers

Randomization is not used in this study.

Volunteers will be enrolled in the study sequentially according to the cohort principle, when the inclusion in each subsequent cohort is made after confirming the safety of the dose of BCD-089 used in the previous cohort (a detailed description is presented in Section “Design”).

[redacted]

The investigator records the screening number and study site number in the source documentation and CRF.

JSC BIOCAD maintains lists of screening and identification numbers of all volunteers enrolled in the study.

4.4. Description of doses and dosing regimens of the study drugs Description of the dosage form and labeling of the study drugs

4.4.1. Description of doses and dosing regimens of the study drugs

Study No. BCD-089-1 includes seven cohorts:

1. Cohort 01 - 1 volunteer to whom a single subcutaneous injection of BCD-089 at a dose of 0.06 mg/kg will be administered.
2. Cohort 02 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.3 mg/kg will be administered.
3. Cohort 03 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.625 mg/kg will be administered.
4. Cohort 04 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.0 mg/kg will be administered.
5. Cohort 05 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.6 mg/kg will be administered.
6. Cohort 06 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.2 mg/kg will be administered.
7. Cohort 07 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.9 mg/kg will be administered.

A guidance for preparation of the solution for injection and the table of dose calculations and administration volumes depending on the volunteer's body weight are presented in a separate manual for performing BCD-089 injections.

The inclusion of volunteers in the study is sequential. The first to participate in the study is one volunteer, representing the cohort "01", who was administered a single subcutaneous injection of BCD-089 at a dose calculated with an additional safety factor relative to the safe starting dose - 0.06 mg/kg. In the absence of grade 3-4 adverse events related to the test product, developing within the first 7 days after the injection, three volunteers are included in cohort 02. Further, the volunteer inclusion algorithm corresponds to the following general principle:

In the absence of any grade 3-4 AEs (DLT) associated with the test product within 7 days after the injection, the next cohort of three volunteers with dose escalation is included in the study - cohort 02 (cohort 03, cohort 04, etc.).

If grade 3-4 AEs (DLT) associated with the test product are recorded in only one volunteer in a cohort of three volunteers, three more healthy volunteers are additionally included in this cohort.

With the development of grade 3-4 AEs (DLT) associated with the test product in two of six volunteers, the dose at which this event was recorded will be taken as the maximum tolerated dose, further dose escalation will be ceased.

4.4.2. Description of the dosage form and labeling of the study drugs

Test drug: BCD-089 (JSC BIOCAD, Russia)

Pharmaceutical form: solution for injection.

Composition per mL:

Active substance: [redacted]

Excipients:

[redacted]

Manufacturer: JSC BIOCAD, Russia

Packaging:

[redacted]

Labeling:

[redacted]

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[redacted]

Composition per mL:

[redacted]

Manufacturer: JSC BIOCAD, Russia

Shelf life: 2 years.

Storage and transportation conditions:

[redacted]

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Packaging:

[redacted]

Labeling:

[redacted]

4.5. Expected duration of study and subject participation in the study

The estimated duration of the study is 7 months, including volunteers recruitment (up to 2 months), period of administration of the study drugs and follow-up of study participants, data collection and statistical analysis of the results. The expected duration of participation of each subject in the study is up to 85 weeks, including the screening period (up to 2 weeks) and the active phase of the study (71 days).

4.6. Description of sequence and duration of all study periods

4.6.1 Schedule of study visits and procedures

The schedule of visits and their conduct are similar for the volunteers in all cohorts. A 14-day screening examination and 13 subsequent visits are planned to be conducted during the study. The first day of the study is the day of the first administered of BCD-089. The subsequent visits are calculated relative to the first BCD-089 administration. The frequency and timing of the study procedures are shown in Table 7.

Table 7. Listing and frequency of investigations and clinical examinations.

Study type	Control parameters	Frequency
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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Study type	Control parameters	Frequency
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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Table 8. Listing and frequency of laboratory tests

Study type	Control parameters	Frequency	Location
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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Study type	Control parameters	Frequency	Location
		[redacted]	
[redacted]	• [redacted]	[redacted]	[redacted]
[redacted]	• [redacted]	[redacted]	[redacted]
[redacted]	• [redacted]	[redacted]	[redacted]
[redacted]	[redacted] • [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 9. Study flowchart.

Visit number	**scre enin g**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 8**	**Day 11**	**Day 15**	**Day 22**	**Day 29**	**Day 50**	**Day 71**
Day from the first injection	-14	0	1	2	3	4	5	7	10	14	21	28	49	70
Signing the Informed Consent Form	+													
Clinical and demographic data collection	+													
Assessment of vital signs	+	+[2]						+		+	+	+	+	+
Height measurement	+													
Body weight measurement	+	+												
Physical examination	+	+						+		+	+	+	+	+
Chest photofluorography	+													
Pain assessment using VAS		+	+											
Complete blood count	+							+		+		+		+
[redacted]														
[redacted]														

[2] On day 1, the assessment of vital signs is performed prior to administration of the drug and 1 hour after it.

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Visit number	**scre enin g**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 8**	**Day 11**	**Day 15**	**Day 22**	**Day 29**	**Day 50**	**Day 71**
Day from the first injection	-14	0	1	2	3	4	5	7	10	14	21	28	49	70
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■	■
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Blood chemistry test	+							+		+		+		+
Blood tests for infection markers	+													
Urinalysis	+							+						+
Alcohol breath test	+													
Urine drug test (psychotropic drugs, psychoactive medications)	+													
ECG	+							+						+
Study drug injection		+												
Concomitant therapy data collection	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Recording of injection site reactions		+[3]	+		+			+		+		+		+

[3] On Day 1, an assessment of injection site reactions is performed prior to administration of the drug and 8 hour after it.

Visit number	**screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Visit		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 8**	**Day 11**	**Day 15**	**Day 22**	**Day 29**	**Day 50**	**Day 71**
Day from the first injection	-14	0	1	2	3	4	5	7	10	14	21	28	49	70
AE/SAE recording	+[4]	+	+	+	+	+	+	+	+	+	+	+	+	+

[4] Only SAEs should be registered at the screening.

4.6.2. Description of individual study visits

[redacted]

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[redacted]

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[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

4.6.3. Description of individual clinical, laboratory, and imaging assessments

4.6.3.1. Physical examination

Physical examination must include the assessment of the following organs and systems:

- Skin and visible mucous membranes (visual inspection)
- Lymph nodes (visual inspection, palpation)
- ENT organs, respiratory system (visual inspection, lung auscultation)

- Cardiovascular system (heart auscultation, examination of the area of the major vessels)
- GI tract assessment (visual inspection, abdomen palpation)
- Assessment of the liver size (palpation, percussion)
- Assessment of the spleen size (palpation, percussion)
- Genitourinary tract assessment (percussion over the area of the kidneys, urinary bladder)
- Nervous system (meningeal signs, focal neurologic deficits)
- Mental status examination (signs of depression, suicidal tendencies, acute psychotic disorder)

4.6.3.2. Clinical and demographic data collection, history of drug therapy

The following data on the volunteer should be recorded at the screening:

- Date of birth
- Sex
- Age
- Assessment of child-bearing potential (birth control methods use, data on sterilization if applicable)
- Collection of past medical history (infectious diseases, general disorders, surgery etc.)
- Collection of history of drug therapy: medicinal products that the volunteer had been taking within 30 days before the screening specifying the dose, dosing frequency, duration of treatment, reasons for discontinuation (if applicable)

4.6.3.3. Assessment of vital signs

Vital sign assessment includes measurement of axillary body temperature (in degrees Celsius), measurement of blood pressure (on one arm, in mmHg), pulse rate at the wrist.

4.6.3.4. Complete blood count, blood chemistry, and urinalysis

Standard complete blood count testing methods shall be used under fasting conditions (8 hours without food). Test material – venous blood, volume drawn – at least 2 mL. This test includes the measurement of the following hematologic parameters:

- Hemoglobin, g/L

- Red blood cells (cells $\times 10^{12}$/L)
- Platelets (cells $\times 10^{9}$/L)
- White blood cells (cells $\times 10^{9}$/L)
- Neutrophils (cells $\times 10^{9}$/L)
- Lymphocytes (cells $\times 10^{9}$/L)
- Erythrocyte sedimentation rate (mm/h)

Standard blood chemistry testing methods are used under fasting conditions (8 hours without food, including sweet or alcoholic beverages). Test material – venous blood, volume drawn – at least 4 mL. The test includes determination of the following parameters:

- Total protein (g/L)
- Glucose (mmol/L)
- ALT (U/L)
- AST (U/L)
- Total bilirubin, μmol/L
- Creatinine, μmol/L

Standard urinalysis shall be performed with assessment of physical, chemical properties and sediment microscopy.

4.6.3.5. Blood test for infection markers

HIV tests include the qualitative assessment of type 1 and 2 anti-HIV antibodies (HIV Ag/Ab Combo) in blood serum or plasma.

Screening syphilis tests include an anti-cardiolipin test (RPR-test) in blood serum.

The presence of hepatitis B infection is assessed based on the results of blood serum or plasma HBsAg testing. The presence of hepatitis C infection is assessed based on total anti-HCV antibody test results.

All the investigations above are conducted in accordance with the standard procedure used at the study site laboratory or central laboratory. Blood volume needed is 6 mL.

4.6.3.6. Determination of BCD-089, IL-6 receptor, C-reactive protein, IL-6 concentrations

4.6.3.6.1 Determination of BCD-089 concentrations

[redacted]

Table 10. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

4.6.3.6.2 Determination of Interleukin-6 concentrations

[redacted]

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Table 11. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

4.6.3.6.3 C-Reactive protein concentration determination

[redacted]

Table 12. [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

4.6.3.6.4 Determination of soluble IL-6 receptor concentration

[redacted]

Table 13. [redacted]

[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

4.6.3.7. [redacted]

[redacted]

[redacted]

4.6.3.8. Receptor occupancy assay

[redacted]

[redacted]

Figure 9. [redacted]

[redacted]

4.6.3.9. Chest photofluorography

Chest photofluorography is performed to exclude lung disorders using the method adopted at the study site. If necessary, the Sponsor's representative may request the scans (if active tuberculosis develops during participation in the study).

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4.6.3.10. Electrocardiography

Standard 12-lead ECG is performed.

4.6.3.11. Assessment of injection-related pain by a volunteer

The tenderness assessment is performed immediately after the injection or on Day 2 and is performed by a volunteer independently by filling in a special 10-point visual scale (see below) For each injection site (if there were several injections), a separate scale should be filled in to assess the pain.

Figure 10. Point Scale for Pain Assessment

Instruction: this scale reflects how much pain you have experienced during the drug injection. "0" means no pain, "10" - the maximum possible, almost unbearable pain.

4.6.3.12. Assessment of injection site reactions

Injection site reactions are recorded in a separate Injection Site Reaction Registration Form (see Appendix 1). If several injections have been performed, each injection site should be evaluated separately.

[redacted]

4.6.3.13. Technique of performing BCD-089 injections

[redacted]

[redacted]

4.6.3.13. Urine drug test (psychotropic drugs, psychoactive medications)

It is performed once during screening by immunochromatography (using test strips) and is aimed at searching for traces of the use of amphetamine, marijuana, morphine, cocaine (and its metabolites), and methamphetamine. If the test results are positive or doubtful for any of the listed substances, the volunteer must not be included in the study.

4.6.3.14. Alcohol breath test (quantitative)

The study is performed once at a screening using a certified breathalyzer mentioned in the State register of measuring instruments, with a sensitivity range of 0.00-2.50 mg/mL. If the test results are positive for any of the listed substances, the volunteer must not be included in the study.

4.6.3.15. Unscheduled visits

If adverse events occur, the volunteer may come for an unscheduled visit to conduct additional safety tests which should mandatorily include data collection on concomitant medication, physical examination, BP, body temperature measurements, complete blood count, blood biochemistry, urinalysis, and/or other tests deemed necessary by the Investigator.

4.7. Description of Interruption Rules or Early Withdrawal Criteria for individual subjects, study parts, or the study in general

Volunteers will be excluded from further participation in the study in the following cases:

1. Identification, after the volunteer's inclusion in the study, of gross violations of inclusion/non-inclusion criteria (as decided by JSC BIOCAD)[5];
2. Patient's withdrawal of the consent to participate in the study;
3. AEs and SAEs, laboratory abnormalities or concomitant diseases, when, in the opinion of the investigator or Sponsor, the continuation of the study treatment is impossible or dangerous for the volunteer, or is not in the best interests of the volunteer, or is unsafe;
4. The volunteer misses more than 1 doses of BCD-089 (in this case, the withdrawal of such a patient will have to be agreed with representatives of JSC BIOCAD);
5. The patient has a major depressive disorder or suicidal ideation or makes suicidal attempts;
6. If the study is terminated by the decision of JSC BIOCAD, local Ethics Committee, or regulatory bodies;
7. In case of the use of drugs prohibited by the Protocol;

[5]Deviations from the eligibility criteria, which are justified by the Investigator and agreed by the Sponsor, are not a reason to exclude the patient from the study.

8. In case of the volunteer's death.

The Investigator has to inform JSC BIOCAD about the volunteer's premature withdrawal and the reasons of premature withdrawal within 24 hours.

If a volunteer is withdrawn from the study, the Study Completion Form in the CRF must be completed. Follow-up procedures of prematurely withdrawn patients are described in Section 5.4.

See Section 11.5 "Study Termination" below for further details.

4.8. Drug accountability procedures used in the study

The Investigator is responsible for study drug accountability. The Investigator must keep accurate records of the drugs throughout the study, in compliance with regulatory requirements. The Investigator must document the supply of drugs from JSC BIOCAD.

When the Investigator or a pharmacist receives the drugs, he/she must check the received lot, sign and date the form of drug supply and the documentation provided by JSC BIOCAD, and then return it to JSC BIOCAD. Copies of these documents must be stored in the Investigator's File.

The amount of supplied drugs must be recorded in the Drug Accountability Form provided by JSC BIOCAD, which then may be used as a balance sheet for the investigational product.

Accurate accountability records must be made available to the monitor for verification at each monitoring visit. Drug accountability records must include:

- Confirmation of supply to the study site;
- Inventory at the study site;
- Use of drugs by each study subject;
- Return to JSC BIOCAD of unused products.

Records must also include the date, amount, batch number, lot number and expiry date (if applicable). The Investigator must keep records to ensure that:

- The study participants must be provided with the doses established by the Protocol/amendment;
- All the investigational products supplied by JSC BIOCAD was fully checked, delivered in full and undamaged.

Any unused investigational product must be restricted from use for any other purposes outside this study.

A monitor of JSC BIOCAD will collect drug accountability reports on a regular basis.

4.8.1. Handling of products used in the study

At study sites, the test drug must be stored in a refrigerator at 2 to 8°C in a place that may only be accessed by the Principal Investigator, co-investigators and an authorized administrative representative of the healthcare facility, who is provided with access according to local rules.

The product may be stored only at the official study site involved in this study. The Investigator must ensure safe product storage, preventing its loss, theft or inappropriate storage conditions (temperature) required by the Sponsor and specified in the Investigator's Brochure. The Investigator is required to keep a temperature log.

4.9. Study numbers storage and unblinding procedure

The drug will be used in an open-label mode so the unblinding procedure is not envisaged.

4.10. List of all data recorded directly in the CRF (i.e., without prior written or electronic entry) and regarded as source data

All data that must be recorded in the CRF must be present in the source documents of the study site.

Data that is not subject to registration in the source documents should not be included in the CRF.

5. SELECTION AND EXCLUSION OF STUDY PARTICIPANTS

5.1. Inclusion criteria

1. Signed informed consent;
2. Male;
3. Age 18 - 45 years inclusive;
4. Body mass index (BMI) within normal limits (18.5 - 30.0 kg/m^2);
5. A verified diagnosis of "healthy", established according to the medical history, physical examination and laboratory data:

- absence in the history and at the time of the screening examination of clinically obvious impaired function of the cardiovascular, respiratory, nervous, hematopoietic, endocrine, gastrointestinal systems, liver and kidneys;
- absence of history of cardiovascular diseases;
- complete blood count, blood chemistry, and urinalysis results are within reference ranges adopted at the study site;
- hemodynamic parameters within normal limits: SBP - within 100 - 120 mm Hg., DBP - within 60 - 80 mm Hg. Art., heart rate - 50 - 90 bpm;
- absence of chronic infections (tuberculosis) or history of chronic inflammatory diseases;
- absence of laboratory markers of hepatitis B, C, HIV and syphilis;
- absence of acute infectious diseases within 4 weeks before inclusion in the study;
- absence of mental disorders and any other conditions that can affect the ability of the participant to follow the requirements of the protocol, including depression;
- satisfactory well-being (in the opinion of the volunteer) within 30 days before signing of the informed consent form;

6. Absence of evidence of alcohol abuse or drug addiction at the time of inclusion in the study or in medical history, as well as negative results at the screening alcohol breath test, together with a negative result of the urine drug test;
7. The ability of the volunteer to follow the Protocol procedures, in the Investigator's opinion;
8. The willingness of volunteers and their sexual partners of childbearing potential to use reliable methods of contraception, starting 2 weeks before inclusion in the study and throughout the study (day of injection and 70 days from the date of its administration). This requirement does not apply to participants who underwent surgical sterilization. Reliable methods of contraception involve the use of 1 barrier method in combination with one of the following: spermicides, intrauterine device/oral contraceptives for the sexual partner;
9. Willingness not to drink alcohol within 24 hours before the administration of the test product and for 8 days after.

1.2. Exclusion criteria

1. A history of use of monoclonal antibody products against interleukin-6 or its receptor;
2. Allergy history (anaphylactic shock or multidrug allergy);
3. Known allergy or intolerance to monoclonal antibody drugs (murine, chimeric, humanized, or human) or any other components of the study drug.
4. Major surgery less than within 30 days prior to signing the informed consent form;
5. Severe infections (including those that required hospitalization or parenteral antimicrobial/antimycotic/antiviral/antiprotozoal treatment) within 6 months before signing the ICF;
6. Systemic antimicrobial/antimycotic/antiviral/antiprotozoal treatments within 2 months before signing the ICF;
7. More than 4 episodes of respiratory infections within 6 months before signing the informed consent form;
8. Impossibility to insert a venous catheter for blood sampling (for example, due to skin diseases at venipuncture sites);
9. Diseases or other conditions that can affect the pharmacokinetics of the test product (e.g., chronic liver, kidney, blood, cardiovascular, bronchopulmonary and neuroendocrine systems disorders (including diabetes mellitus) etc.);
10. A history of fever above 40°C;
11. A history of episodes of elevated hepatic transaminases above 2.5 x ULN;
12. Epileptic seizures, history of seizures;
13. Current depression or a history of depression, suicidal thoughts/attempts at the time of the screening examination or a history of such behavior;
14. Regular use of any oral or parenteral medications, including over-the-counter drugs, vitamins, and dietary supplements within less than 2 weeks before signing the informed consent;
15. Use of medications, including OTC drugs that have a pronounced effect on hemodynamics, liver function, etc. (barbiturates, omeprazole, cimetidine, etc.) within less than 30 days before signing the informed consent form;
16. Use of medicinal products that affect the immune status (cytokines and their inducers, glucocorticoid hormones, etc.) within less than 2 months prior to signing the informed consent form;

17. Vaccination within 4 weeks prior to signing of informed consent form;
18. Values of standard laboratory tests and investigations results that are beyond the reference ranges;
19. Smoking more than 10 cigarettes per day;
20. Consumption of more than 10 units of alcohol per week (1 unit of alcohol is equivalent to ½ liter of beer, 200 mL of wine or 50 mL of liquor) or a history of alcoholism, drug addiction or drug abuse;
21. Donation of 450 mL or more of blood or plasma within 2 months prior to signing of the informed consent form;
22. Participation in other clinical studies within less than 2 months before signing the informed consent form or simultaneous participation in other clinical studies;
23. Prior participation in this clinical study.

5.3. Exclusion criteria

Volunteers will be excluded from further participation in the study in the following cases:

1. Identification, after the volunteer's inclusion in the study, of gross violations of inclusion/non-inclusion criteria (as decided by JSC BIOCAD);
2. Patient’s withdrawal of the consent to participate in the study;
3. AEs and SAEs, laboratory abnormalities or concomitant diseases, when, in the opinion of the investigator or Sponsor, the continuation of the study treatment is impossible or dangerous for the volunteer, or is not in the best interests of the volunteer, or is unsafe;
4. The volunteer misses more than 1 doses of BCD-089 (in this case, the withdrawal of such a patient will have to be agreed with representatives of JSC BIOCAD);
5. The patient has a major depressive disorder or suicidal ideation or makes suicidal attempts;
6. If the study is terminated by the decision of JSC BIOCAD, local Ethics Committee, or regulatory bodies;
7. In case of the use of drugs prohibited by the Protocol;
8. In case of the volunteer’s death.

The investigator had to inform JSC BIOCAD about his premature withdrawal and the reasons of premature withdrawal within 24 hours.

5.3.1. Substitution of volunteers who withdrew from the study

The volunteers can be substituted in the following cases:

1. Volunteers who withdrew the study for reasons not related to administration of the study drug (missing visit, withdrawal of consent, systematic violation of visit windows, etc.).
2. Non-compliant volunteers (see Section 6.6).

Volunteers who withdrew from the study after administration of the study drug for safety reasons (AE that did not allow to come to a visit to perform the Protocol procedures) will not be replaced.

5.4. Follow-up of subjects who withdrew from the study

Follow-up of volunteers who received at least one dose of the drug

In case of early withdrawal of a volunteer after administration of the study drug, it is required to conduct an “Early Withdrawal Visit” and fill out an “Early Withdrawal Form”.

If a patient is discontinued from the study due to an AE/SAE, the Investigator should continue his/her management and follow-up after the “Early Withdrawal Visit” in accordance with the standard practices used at the study site for AE/SAE treatment. The volunteer will be followed up until full resolution of the AE or SAE.

6. USE OF THE TEST DRUG

6.1. Dosing regimen tested

Study No. BCD-089-1 includes seven cohorts:

1. Cohort 01 - 1 volunteer to whom a single subcutaneous injection of BCD-089 at a dose of 0.06 mg/kg will be administered.

2. Cohort 02 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.3 mg/kg will be administered.
3. Cohort 03 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 0.625 mg/kg will be administered.
4. Cohort 04 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.0 mg/kg will be administered.
5. Cohort 05 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 1.6 mg/kg will be administered.
6. Cohort 06 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.2 mg/kg will be administered.
7. Cohort 07 - a maximum of 6 volunteers to whom a single subcutaneous injection of BCD-089 at a dose of 2.9 mg/kg will be administered.

The inclusion of volunteers in the study is sequential. The first to participate in the study is one volunteer, representing the cohort “01”, who is administered a single subcutaneous injection of the estimated maximum safe dose of BCD-089 - 0.06 mg/kg. In the absence of grade 3-4 adverse events related to the test product, developing within the first 7 days after the injection, three volunteers are included in cohort 02. Further, the volunteer inclusion algorithm corresponds to the following general principle:

In the absence of any grade 3-4 AEs (DLT) associated with the test product within 7 days after the injection, the next cohort of three volunteers with dose escalation is included in the study - cohort 02 (cohort 03, cohort 04, etc.).

If grade 3-4 AEs (DLT) associated with the test product were recorded in only one volunteer in a cohort of three volunteers, three more healthy volunteers will be additionally included in this cohort.

With the development of grade 3-4 AEs (DLT) associated with the test product in two of six volunteers, the dose at which this event was recorded will be taken as the maximum tolerated dose, further dose escalation will be ceased.

6.2. Investigational product dose correction

Not planned.

6.3. Overdose

[redacted]

6.4. Concomitant therapy, allowed and prohibited medications

In the course of the study, the volunteers must not use any additional medicinal products (besides those specified in the study design).

In this study, there are no specific restrictions on medications for intercurrent diseases and conditions that a volunteer might have during the study period. In case of disorders that occur during the study, the volunteers can receive full supportive care in accordance with standard guidelines.

6.5. Methods of monitoring adherence to study procedures

Information about drug administration, doses, and between-visit intervals will be documented during the study.

Clinical Studies Specialist will review the accountability documents during monitoring visits and at the end of the study.

6.6. Compliance assessment

In this clinical study, any volunteer is considered to be non-compliant if he:

- Missed more than one visit;
- Deviated from the scheduled window for more than one visit;
- Missed sampling of more than 2 blood samples for evaluation of pharmacokinetics and pharmacodynamics;
- Deviated from the scheduled window for pharmacokinetic and pharmacodynamic sampling by a time exceeding the acceptable deviation described in Tables 3 and 4.

7. PHARMACOKINETICS AND PHARMACODYNAMICS ASSESSMENT

7.1 List of pharmacokinetic variables

To evaluate PK parameters of the drugs based on the data obtained on the concentration of anti-IL-6 receptor monoclonal antibody in the blood of volunteers, the following pharmacokinetic parameters will be calculated: the area under the "concentration-time" curve (AUC from the moment of administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity), the maximum concentration of anti-IL-6 receptor monoclonal antibody in human serum, C_{max}, time to reach the maximum concentration, T_{max}, half-life, T½, the elimination constant Kel and total clearance, CL, after a single-dose subcutaneous injection of the test drug. The values of the Cmax and Tmax will be calculated as the highest of the measured concentration values and the corresponding time of the observed maximum. The $AUC_{(0-t)}$ will be calculated using the logarithmic trapezoid method. The value of $AUC_{(0-\infty)}$ will be determined by the formula: $AUC_{(0-\infty)}$ = AUCt+CT/kel, where AUCt is the area under the "concentration-time" curve from the moment of drug administration to the last measured BCD-089 concentration (in this study it is AUC (0-1680h)), Ct and Kel are the calculated values of the drug concentration in the last sample (in this study – C1680h) and the elimination constants, respectively. To calculate Ct and Kel, the final (monoexponential) section of the pharmacokinetic curve is described using nonlinear regression analysis.

Thus, the main PK parameters evaluated will include:

Primary:

- ✓ AUC_{0-1680} - area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity).

Secondary:

- ✓ C_{max} (maximum serum concentration of anti-IL-6 receptor antibody);
- ✓ T_{max} (time to maximum concentration);
- ✓ $T_{½}$ (half-life),
- ✓ K_{el} (elimination rate constant),
- ✓ CL (total clearance).

7.2 List of pharmacodynamical parameters

To evaluate PD parameters of the drugs based on the data obtained on the concentration of soluble IL-6 receptor, as well as CRP level in the blood of volunteers, the following pharmacokinetic parameters will be calculated: the area under the "concentration-time" curve (AUC from the moment of administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity), the maximum concentrations of the aforementioned markers in human serum, C_{max}, time to achieve maximum concentration, T_{max} (C_{min} and T_{min} for C-reactive protein) following a single-dose subcutaneous administration of the test drug. The values of the Cmax and Tmax will be calculated as the highest of the measured concentration values and the corresponding time of the observed maximum. The values of the C_{min} and T_{min} will be calculated as the lowest of the measured concentration values and the corresponding time of the observed minimum. The $AUC_{(0-t)}$ will be calculated using the logarithmic trapezoid method. The value of $AUC_{(0-\infty)}$ will be determined by the formula: $AUC_{(0-\infty)}$ = AUCt+CT/kel, where AUCt is the area under the "concentration-time" curve from the moment of drug administration to the last measured CRP, IL-6 and sIL-6R concentrations (in this study it is AUC (0-1680h)), Ct and Kel are the calculated values of the drug concentration in the last sample (in this study – C1680h) and the elimination constants, respectively. To calculate Ct and Kel, the final (monoexponential) section of the pharmacokinetic curve is described using nonlinear regression analysis.

Thus, the main PD parameters evaluated will include:

1. C-reactive protein concentration determination:

Primary:

- ✓ AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity).

Secondary:

- ✓ C_{min} (minimum detectable concentration in blood serum),
- ✓ T_{min} (time to minimum serum concentration).

2. Determination of IL-6 concentration, soluble IL-6 receptor concentration:

Primary:

- ✓ AUC_{0-1680} (area under the concentration-time curve from the administration of the drug to 1680 h (71 days after administration) and $AUC_{0-\infty}$ (to infinity).

Secondary:

- ✓ C_{max} (maximum concentration in serum),
- ✓ T_{max} (time to maximum serum concentration).

Based on the results of flow cytometry, the following parameters will be calculated (a pilot study, it is not the endpoint)

- ✓ Percentage of occupancy of IL-6 receptors with BCD-089 2 hours after drug administration, as well as in 168, 336 and 504 hours.

[redacted]

8. SAFETY ASSESSMENT

List of safety parameters

To assess the safety of the study therapy, the following parameters (secondary endpoints) will be used:

- ✓ Proportion of subjects who developed SAEs in each cohort.
- ✓ Proportion of subjects who developed AEs in each cohort.
- ✓ Proportion of subjects who developed injection site reactions in each cohort.
- ✓ Proportion of subjects who developed grade 3-4 AEs in each cohort.
- ✓ Proportion of subjects who developed any grade neutropenia in each cohort.
- ✓ Proportion of subjects who discontinued the study due to AEs and SAEs in each cohort.

8.2 Definitions

8.2.1 Adverse Events

Adverse event (AE): Any untoward medical event occurring in a participant of a clinical study after the administration of a medicinal product, which can have no causal relationship with the administration of the drug.

An AE is any untoward and unintended sign (including an abnormal laboratory finding), symptom, or disease, the time of occurrence of which does not exclude a causal relationship with the use of the drug, regardless of whether it is related or not, from the start of the study drug administration until day 28 inclusive after withdrawal of the volunteer from the clinical study.

As part of this study, the Investigator had to register all AEs, starting from grade 1 according to the classification, regardless of their clinical significance.

8.2.2 Serious adverse events

Serious adverse event (SAE) is any untoward medical event, regardless of the dose of the drug:

- Results in death;
- is life-threatening;
- requires hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly or birth defect.

[redacted]

[redacted]

8.3 Methods and timeframes for the assessment, recording, and analysis of safety parameters

8.3.1 Timeframes for the assessment of safety parameters

Information about serious adverse events will include data on SAEs occurring from the moment of signing the ICF and until the patient stops participating in the study (as planned or prematurely). Information about AEs not meeting the seriousness criteria will be registered from the first administration of the drug and until the volunteer stops participating in the study (as planned or prematurely).

Information about all SAEs will be reviewed immediately starting from the submission of SAE report to the Drug Safety Division of JSC BIOCAD (provided timely notification of the

Investigator in case of SAEs). A pooled analysis of SAEs will be carried out during the preparation of the final study report.

AEs not meeting the seriousness criteria will be analyzed routinely during the preparation of the final study report.

8.3.2 Methods and timeframes for the assessment and registration of safety parameters

Safety analysis will include all volunteers who received the test drug. Cases of SAEs that developed before the test drug administration should also be analyzed.

Safety analysis will be based on:

- data on reported AEs and SAEs;
- physical examination data and vital signs assessment;
- complete blood count, blood chemistry, and urinalysis results;
- electrocardiography results;
- data on cases of injection site reactions.

The frequency of these procedures throughout the study is described in Section 4.6.1 “The schedule of study visits and procedures”. AE/SAE are registered according to the guidance provided by the Sponsor.

The Investigator is responsible for registering the adverse events reported in clinical studies.

AE are registered from the moment of signing the informed consent form and until the volunteer completes his participation in the study (as planned or prematurely). SAEs are registered from the moment of signing the informed consent and until the patient stops participating in the study (as planned or prematurely) as well as for a longer period after the last dosing, if the Investigator believes that this SAE is associated with the use of the drug or any study procedures.

Adverse events (AEs) that do not meet the seriousness criteria are registered by the Investigator in source documents and in the CRF and the records are provided to the clinical study monitor at the next scheduled monitoring visit for evaluation. Serious adverse events (SAEs) must be promptly reported to the Sponsor, within 24 hours. [redacted]

[redacted]

8.4 Requirements for reports, AE registration and reporting procedures, and AE Reporting Form completion

8.4.1 AE/SAE registration

Presence or absence of adverse events during the period from the last visit is evaluated at each visit. Any serious adverse event observed in a volunteer from signing the informed consent form should be registered in source documents and in the dedicated Adverse Event Reporting Form (in eCRF).

Adverse events are registered and numbered consecutively, as they occur. Each AE is reported using the AE Reporting Form. The rules for AE/SAE reporting are described in detail in the Guidance provided by the Sponsor.

Adverse events are registered regardless of seriousness or causal relationship with study therapy. **All AEs are subject to recording in the study, including Grade 1 AEs (CTCAE v.4.03).** If the same adverse event reoccurs (after the previous case resolved), it should be registered as a new adverse event, with a separate number.

8.4.2 AE/SAE Reporting Form completion

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Information about the method and duration of subjects' follow-up after an AE/SAE

If a volunteer is discontinued from the study due to an AE/SAE, the Investigator should continue his/her management and follow-up in accordance with the standard practices used at the study site for AE/SAE treatment. The volunteer will be followed up until full resolution of the AE or SAE. See Section 5.4 for further details.

9. STATISTICAL METHODS

9.1 Calculation of the parameters of pharmacokinetics and pharmacodynamics

9.1.1. Pharmacokinetic parameters

Based on the calculated concentration values for the anti-IL-6 monoclonal antibody in the blood of each volunteer, the following pharmacokinetic variables will be estimated at time points specified in this protocol:

1. **C_{max}** - maximum serum concentration of anti-IL-6 receptor antibody over the observation period.
2. **t_{max}** - time to achieve maximum serum concentration (C_{max}) of anti-IL-6 receptor antibody.
3. **$AUC_{0\text{-}1680}$** –- the area under the concentration of anti-IL-6 receptor monoclonal antibody-time curve over the time interval from 0 to 1680 hours. $AUC_{0\text{-}1680}$ will be calculated using the trapezoid method using the following formula, where Cp is the concentration of the drug BCD-089 in the blood at the time tp in hours:

$$t_p \in \{0; 2; 8; 12; 24; 48; 72; 96; 120; 168; 240; 336; 504; 672; 1176; 1680\}_{p=1,\dots,16}$$

4. **$AUMC_{0\text{-}1680}$** - total area under the curve of the concentration of anti-IL-6 receptor monoclonal antibody multiplied by time over the time interval from 0 to 1680 hours. $AUMC_{0\text{-}1680}$ will be calculated using the following formula:

$$AUMC_{0-1680} = \sum_{p=2}^{16} \frac{(C_p * t_p + C_{p-1} * t_{p-1}) * (t_p - t_{p-1})}{2},$$

$where\ C_p -\ concentration$ of anti − IL − 6 − receptor monoclonal antibody против рецептора ИЛ6

$$in\ the\ blood\ at\ t_p$$

$$t_p \in \{0; 2; 8; 12; 24; 48; 72; 96; 120; 168; 240; 336; 504; 672; 1176; 1680\ \}_{p=1,\ldots,16}$$

5. **Total clearance (Cl)** is a parameter that reflects the volume of test tissue, which is cleared from the anti-IL-6 receptor monoclonal antibody per unit of time and is determined by the ratio of the anti-IL-6 receptor monoclonal antibody dose (*DOSE*) to $AUC_{(0\text{-}1680)}$:

$$CL = \frac{DOSE}{AUC_{0-1680}}$$

6. **Mean residence time (MRT)** of the anti-IL-6 receptor monoclonal antibody molecule in the body will be calculated as the ratio of $AUMC_{0\text{-}1680}$ to $AUC_{0\text{-}1680}$:

$$\mathrm{MRT} = \frac{\mathrm{AUMC}_{0-1680}}{\mathrm{AUC}_{0-1680}}$$

7. **Elimination constant** of the anti-IL-6 receptor monoclonal antibody **(k_{el})** will be determined using the following formula:

$$k_{el} = \frac{1}{MRT}$$

8. **Half-life period** of the anti-IL-6 receptor monoclonal antibody **($T_{1/2}$)** will be determined using the following formula:

$$T_{1/2} = \frac{\ln(2)}{k_{el}} = \ln(2) * MRT$$

9. **The area under the concentration-time curve** for anti-IL-6 receptor monoclonal antibody **over the time interval from 0 to ∞ ($AUC_{0\text{-}\infty}$).**

$AUC_{\mathbf{0}-\infty} = AUC_{0-1680} + \frac{C_{\mathbf{1680}}}{k_{el}}$, where

C_{1680} – concentration of anti-IL-6 receptor antibody over the period equal to 1680 hours after the drug administration.

9.1.2. Pharmacodynamical parameters

Based on the obtained concentrations of C-reactive protein, IL-6 and soluble IL-6 receptor in the blood of each volunteer, the following pharmacodynamic parameters will be calculated at the Protocol-specified time intervals:

1. **C_{max}** – maximum blood concentration of C-reactive protein, IL-6 and soluble IL-6 receptor over the observation period.
2. **t_{max}** – time to maximum blood concentration (C_{max}) of C-reactive protein, IL-6 and soluble IL-6 receptor.
3. **$AUC_{0\text{-}1680}$** – the area under the concentration-time curve for C-reactive protein, IL-6 and soluble IL-6 receptor over the time interval from 0 to 1680 hours. $AUC_{0\text{-}1680}$ is calculated using the trapezoidal method with the following formula:

$$AUC_{0-1680} = \sum_{p=2}^{16} \frac{(C_p + C_{p-1}) * (t_p - t_{p-1})}{2},$$

where C_p *concentration* of C − reactive protein, IL − 6 and soluble IL − 6 receptor values

*ИЛ*6 *in the blood at t moment of time* t_p *(hours),*

$$t_p \in \{0; 2; 8; 12; 24; 48; 72; 96; 120; 168; 240; 336; 504; 672; 1176; 1680\}_{p=1,\ldots,16}$$

4. **C_{min}** – minimum blood concentration of C-reactive protein, IL-6 and soluble IL-6 receptor over the observation period.
5. **t_{min}** – time to minimum blood concentration (C_{min}) of C-reactive protein, IL-6 and soluble IL-6 receptor.

9.2 Statistical analysis methods

The study results will be analyzed using the two-sided statistical hypotheses with a significance level of 0.05.

Quantitative and scale data

To describe quantitative and scale variables, it is planned to use the following characteristics: mean, median, standard deviation, quartiles, minimum and maximum, and coefficient of variance.

The statistical analysis of the obtained data will be conducted using SAS 10.0 software and the R programming language for statistical data processing. Mann-Whitney, Wilcoxon, Kruskal-Wallis, and Friedman tests will be used to compare quantitative and scaled data. The categorical data will be processed using the Fisher's exact test and the χ^2 Pearson test.

Quantitative data include the following parameters:

- Membrane receptor occupancy with BCD-089

Pharmacokinetics:

- Anti-human interleukin-6 receptor monoclonal antibody concentration
- Area under the curve
- Time (including time to maximum concentration, half-life period)
- Elimination characteristics (clearance, elimination constant)

Pharmacodynamics:

- Human IlL-6, C-Reactive Protein, soluble IL-6 receptor concentrations
- Area under the curve
- Time (including time to maximum concentration, trough concentration, time to achieve trough concentration)

Elimination characteristics (clearance, elimination constant)

Tenderness:

Value specified in Visual Analogue Scale (out of 10 points)

Safety:

- Complete blood count parameters
- Blood biochemistry parameters
- ECG parameters
- Urinalysis parameters

- Blood pressure, wrist pulse rate and body temperature
- Size of an abnormal lesion at the injection site reactions
- Time of presence of the abnormal lesion at the injection site

Categorical data include the following parameters:

Pharmacodynamics:

- Proportion of samples showing the maximum signal for membrane IL-6 receptor occupancy

Safety:

- Nature of an abnormal lesion at the injection site
- Frequency of AEs and SAEs by severity grades
- Frequency of grade 3/4 toxicity events
- Frequency of injection-site reactions (total and depending on the type of the lesion)
- Proportion of subjects who developed any grade neutropenia in each cohort.
- Frequency of cases of premature discontinuation from the study due to an AE/SAE

During the analysis, the list of methods used may be extended, if necessary for a high-quality data processing.

9.2. Rationale for the study sample size, including reasoning or calculations to support the statistical power and clinical validity of the study

The calculation of the study sample size was based on the "3 + 3" design and dose levels used in the study.

Volunteers cohort	Dose, mg/kg	Number of mandatory included volunteers	Number of volunteers that can be included in case of DLT development
01	0.06	1	0
02	0.3	3	3
03	0.625	3	3

Volunteers cohort	Dose, mg/kg	Number of mandatory included volunteers	Number of volunteers that can be included in case of DLT development
04	1.0	3	3
05	1.6	3	3
06	2.2	3	3
07	2.9	3	3

9.3. Statistical analysis stages and timeline for reports

The analysis of the results in this clinical trial will be performed upon receipt of all the data planned by the Protocol of the last volunteer included in the study.

9.4. Criteria for study termination

JSC BIOCAD may temporary or permanently stop the study due to issues related to safety, ethics, adherence to protocol, or other reasons. If necessary, JSC BIOCAD will undertake the necessary measures to inform the study site in advance. If the study is temporary or permanently closed, JSC BIOCAD and the Investigator must inform the Ethics Committees and regulatory authorities. In such cases, all study-related data must be submitted to JSC BIOCAD and all unused study drugs must be returned.

9.5. Management of missing, non-evaluable, and uncertain data

[redacted]

9.6. Procedures for reporting any deviations from the initial statistical plan

If the initial clinical study plan must be changed, modifications will be described and explained in the protocol amendment or Interim/Final clinical study report.

9.7 Patient selection for analysis

Demographic data and baseline clinical and laboratory characteristics will be evaluated in all volunteers included in the study.

Safety analysis

Safety analysis will include all volunteers who received the test drug.

Pharmacokinetic analysis

Pharmacokinetics analysis will include data from volunteers who have received BCD-089 and have had no more than two missing/lost/damaged blood serum samples for pharmacokinetics and had no more than two consecutive missing/lost/damaged samples and for whom a serum sample obtained before the test drug administration is available for the analysis.

Pharmacodynamic analysis

Pharmacodynamics analysis will include data from volunteers who have received BCD-089 and have had no more than two missing/lost/damaged of whole blood and/or blood serum for pharmacodynamics studies, and for whom a serum sample obtained before the test drug administration is available for the analysis.

Immunogenicity analysis

Immunogenicity analysis will include data from volunteers who have received BCD-089 and have not had missing/lost/damaged serum samples taken on Days 1 and 71 of the study.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator or the organization involved in the study must allow direct access to the source data/documents for study-related monitoring, auditing, ethical expertise, and inspection carried out by authorized agencies.

11. QUALITY CONTROL AND QUALITY ASSURANCE OF THE STUDY CONDUCT

11.1. Quality guarantees

In accordance with ICH GCP and regulatory requirements, the Sponsor, third parties on its behalf, regulatory authorities or Ethics Committees can conduct audits (inspections) to ensure quality at any time during the study or after the end of the study. The Investigator must provide the auditors direct access to all study-related documents, including source documents, and allocate his/her time and time of his/her team to discuss with auditors the results of audits and inspections, as well as other issues.

11.2. Investigator's adherence to protocol

No deviations from the Protocol are allowed during the study without prior written permission from JSC BIOCAD, except when necessary to prevent any immediate danger to the volunteer.

Protocol deviation is any change, discrepancy, or deviation from the study design or procedures of the study Protocol.

Any protocol deviation in the course of the clinical study must be registered and reflected in the study documents.

All protocol deviations are classified as major or minor deviations.

A minor deviation from the Protocol is an unforeseen and unintended event that occurred during the study and contradicts the requirements of the Protocol, which does not significantly affect the rights, safety and well-being of the volunteer or the consistency, accuracy and reliability of the study data.

A major deviation from the Protocol (or a protocol violation) is a deviation that may affect the rights, safety of a volunteer or the consistency, accuracy, and reliability of the study data.

Examples of probable major protocol deviations:

- A volunteer met study exclusion criteria but was not excluded;
- A volunteer received a prohibited concomitant medication;
- A volunteer was included in the study without meeting the eligibility criteria;
- Study procedures were conducted without obtaining a written informed consent from a volunteer;

- Volunteer's indiscipline, non-compliance with restrictions during participation in the study (taking alcohol, drugs);
- Errors in selection of doses/route of administration/drug storage;
- Protocol violations that may be considered by the clinical trial monitor or study coordinator to have an impact on the safety of participants or the consistency and reliability of the study data;
- Missing two or more of the scheduled blood samples for analysis of pharmacokinetics/pharmacodynamics;
- Any violation of the confidentiality of information about study participants.

Information about major deviations should be presented to the Sponsor and the local ethics committee. In case of any major protocol deviations, the volunteer must be excluded from the final PK/PD data analysis.

The Investigator must have enough time to conduct the study correctly and complete the study within the timeline agreed with JSC BIOCAD, and also have a sufficient number of qualified team members and adequate equipment to perform the procedures specified in this Protocol.

Each co-investigator involved in the study must be familiarized with the Protocol requirements and his/her responsibilities in the study. Delegation by the Principal Investigator of any of his/her responsibilities within this study must be documented in written form in the relevant section of the Investigator's File.

11.3. The Investigator's responsibility for Protocol adherence

[redacted]

[redacted]

11.4. Study monitoring

The monitoring procedures for this study are established in accordance to Standard Operation Procedure of JSC BIOCAD.

[redacted]

11.5. Study termination

JSC BIOCAD may temporary or permanently stop the study due to issues related to safety, ethics, adherence to protocol, or other reasons. If necessary, JSC BIOCAD will undertake the necessary measures to inform the study site in advance. If the study is temporary or permanently closed, JSC BIOCAD and the Investigator must inform the Ethics Committees and regulatory

authorities. In such cases, all study-related data must be submitted to JSC BIOCAD and all unused study drugs must be returned.

12. ETHICS

12.1. Ethical aspects of the study

The study will be conducted in compliance with the ethical principles set forth in the World Medical Association's Declaration of Helsinki "International Ethical Guidelines for Biomedical Research Involving Human Subjects"1964–2008 and ICH GCP rules.

[redacted]

12.2. Confidentiality of study subjects

The Investigator undertakes to maintain confidentiality regarding the identity of volunteers, the text of this Protocol, as well as all other materials and study results.

[redacted]

[redacted]

13.0. DATA MANAGEMENT AND RECORD KEEPING

All study-related documents must be archived at the study site or at the institution's central archive. The list of all study subject identification data must be carefully drafted.

According to ICH GCP definition, the required documents include: signed Protocol and all the amendments, copies of completed CRFs, signed Informed Consent Forms for all volunteers, medical records, diaries and other source documents, approved by ethics committees and regulatory authorities, as well as correspondence with them, including approved documents, drug accountability records, study-related correspondence and the list of volunteers names and addresses. This list is the essential document that should be kept by the Investigator.

The Investigator must keep copies of the required documents for 5 years.

At the end of this period, the Sponsor will inform the Investigator(s) about the date, after which this documents may be destroyed.

The study participant's documentation shall be archived in compliance with the study site rules.

The Investigator must inform the Sponsor about the place of storage of required documents and contact JSC BIOCAD for approval before destroying any of them. The Investigator must prevent accidental or premature destruction of these documents.

14. FUNDING AND INSURANCE

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15. PUBLICATIONS

After the end of the study and statistical processing, its data will be published. The Investigator must not publish the results of this study, including those obtained at his/her study site, without consent from JSC BIOCAD. The results obtained at an individual study site should not be published prior to the publication of overall study results.

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APPENDIX 1. [redacted]