CLINICAL STUDY PROTOCOL

Protocol Title:	An International Multicenter, Randomized, Double-blind, Placebo-Controlled, Dose-finding Clinical Study of Efficacy and Safety of Subcutaneous BCD-085 in Patients with Moderate to Severe Plaque Psoriasis
ClinicalTrials.gov Identifier:	NCT02762994
Protocol ID:	BCD-085-2
Protocol date:	November 16, 2015
Protocol Amendment:	1
Date of Protocol Amendment:	July 12, 2016
Protocol version:	1.1
Study Sponsor/Monitor:	JSC BIOCAD, Russia Legal address: 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, Russian Federation, 198515 Mailing address: Petrovo Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 Tel.: [redacted]; Fax: [redacted]
Sponsor's contact person responsible for signing the Protocol and Protocol amendments:	[redacted] Address: JSC BIOCAD, Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 E-mail: [redacted] Tel.: [redacted]
Sponsor's responsible medical officer:	[redacted] Address: JSC BIOCAD, 34 A, Ul. Svyazi, Strelna, Petrodvortsoviy District, Russian Federation, 198515 E-mail: [redacted] Tel.: [redacted]; [redacted]

The information presented in this document is confidential and intended to be used solely by investigators, ethics committee members, and health care authorities. This information may not be transferred to any third party without the prior written permission from JSC BIOCAD, except when necessary for obtaining patient's consent to participate in the study.
These requirements come into effect upon signature of this Protocol.

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SIGNATURE PAGE

To Protocol version 1.1 of July 12, 2016: An International Multicenter, Randomized, Double-blind, Placebo-Controlled, Dose-finding Clinical Study of Efficacy and Safety of Subcutaneous BCD-085 in Patients with Moderate to Severe Plaque Psoriasis

I, the undersigned, agree with the following:

1. I have read the Protocol, I agree with all the provisions of the Protocol, and I will conduct the trial in compliance with the Protocol, and applicable regulatory requirements of the participating countries.
2. I will ensure no deviations from the Protocol to take place without prior written agreement from the Sponsor and documented approval from local ethics committees of participating countries, except where necessary to eliminate an immediate hazard to the study participants.
3. I confirm that all staff members are appropriately qualified to conduct the study, the study site has all necessary equipment, and I, the study investigator, have sufficient time to conduct this study in accordance with the Protocol
4. I will take all due measures to ensure that all staff members involved in the study are informed about their obligations in accordance with this Protocol.
5. I agree to fully cooperate with audits and inspections conducted in accordance with the rules established by the Sponsor and the state regulatory authorities.
6. I understand that the text of this Protocol and all other materials and results of this study are confidential and proprietary to the Sponsor. I agree not to disclose any of this information to a third party unless required to do so by the law of the participating countries.

Principal Investigator:

_____
Signature

_____
Full Name

_____
Date

[redacted] Vice President R&D, JSC BIOCAD

_____
Signature

_____
Date

ABBREVIATIONS

AE	Adverse event
AlkPh	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
[redacted]	[redacted]
[redacted]	[redacted]
BAbs	Binding antibodies
BCD-085	A monoclonal anti-IL17 antibody manufactured by JSC BIOCAD
BP	Blood pressure
BSA	Body surface area affected by psoriasis
CHF	Congestive heart failure
Cl	Total clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBcor	Hepatitis B core antigen
HBsAg	Surface antigen of hepatitis B virus
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HR	Heart rate
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IMU	Instruction for Medical Use
INN	International non-proprietary name
IU	International unit
JSC	Joint Stock Company
LDH	Lactate dehydrogenase
MAb	Monoclonal antibody
MRT	Mean residence time
NAb	Neutralizing antibodies
NAPSI	Nail Psoriasis Severity Index
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
POA	Percentage of oval area
RAMS	Russian Academy of Medical Sciences
RNA	Ribonucleic acid
SAE	Serious adverse event
SF-36	Short Form Health Survey
SOP	Standard Operating Procedure
sPGA	Static Physicians Global Assessment
SRI	Scientific Research Institute

t½	Elimination half-life
TNF-α	Tumor necrosis factor alpha
TO	Thoracic organs
VAS	Visual analogue scale
Vd	Volume of distribution
WHO	World Healthcare Organization

TERMS AND DEFINITIONS

Term	Definition
Investigational product	This term includes the test drug, comparator, or placebo. It is a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use
Study/test product/drug	A pharmaceutical form the properties of which are investigated in this clinical trial.
Comparator/reference product/drug	An active control being tested as a control in the clinical study to reduce the bias of assessments, keep the study therapy blind, and assess the internal validity of the study and/or comparative effects of the study product.
Case Report Form (CRF)	A printed or electronic document designed to record all the protocol-required information to be reported to the Sponsor on each study subject.
Investigator's Brochure	A compilation of the clinical and non-clinical information on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.
Subject identification code / subject ID |__|__|-|__|__|__|	It is a unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data. Usually, the subject ID is a five-digit code where the first two digits are the site number and the last three digits are assigned sequentially to each participant as he/she enters the study.
Screening number |__|__|-|__|__|__|	A unique code assigned to each study subject who have signed the informed consent. The first two digits are the site number, and the last three digits are assigned sequentially to each patient as he/she gets enrolled at this particular study site.
Randomization number	A unique number assigned to each patient included in the study (randomized) and coding a specified therapy. After randomization, this number is not used anywhere.
Evaluation	The procedure of obtaining the data that have to be gathered in this trial.
Inclusion in the study	The time point corresponding to randomization and assigning to therapy groups.
Other therapy used in the study	Any medications other than the investigational product that are used to perform the study procedures. This includes, for example, the drugs used as part of the combination therapy.

Term	Definition
Early discontinuation / withdrawal	The time point when the patient continues participation in the study before the planned investigational treatment is completed and/or assessments are performed. No further assessments are performed beyond this point except for monitoring of the survival and/or disease progression in certain trials. If the patient discontinues the study due to an event planned by the Protocol (for example, a complete response), he/she is considered a dropout anyway.
End-of-study	The time point when the patient attends his/her last study visit.
Study therapy	Any medication or a combination of medications used in any arm as part of study procedures, including concomitant medications and introductory therapy before the active medication.
Concomitant therapy	Therapy with any drugs included in the study therapy, except for the test drug and reference drug. For example, drugs used for combination therapy, pre-medication etc.
Termination of investigational therapy	The time point corresponding to the permanent discontinuation of the study therapy regardless of the reason. It can correspond (or not) to the time point of the premature patient's withdrawal
Variable	An identifier used for the data analysis and derived directly or indirectly from the protocol-specified assessments at pre-determined time points.

DOCUMENT HISTORY

N/A.

Names/positions of investigators responsible for the study conduct. Contact information of the study sites

#	Principal Investigator (full name, and job title)	Name of study (clinical) site	Address and phone of study (clinical) site
Medical institutions in the Russian Federation			
1.	[redacted]	State Budgetary Moscow Healthcare Institution Moscow Research and Applied Center for Dermatology and Cosmetology of Moscow Healthcare Department	17, Leninskiy Pr., Moscow, Russia, 119071 Phone: [redacted]
2.	[redacted]	State Budgetary Healthcare Institution Chelyabinsk Regional Clinical Dermatology and Venereology Dispensary	24, Ul. Yablochkina, Chelyabinsk, Russia, 454092 Phone/Fax: [redacted]
3.	[redacted]	State Budgetary Educational Institution of Higher Professional Education Irkutsk State Medical Academy of the Ministry of Healthcare and Social Development of the Russian Federation	1, Ul. Krasnogo Vosstaniya, Irkutsk, Russia, 664003 Phone: [redacted]
4.	[redacted]	State Budgetary Educational Institution of Higher Professional Education N.N. Pirogov Russian National Research Medical University of the Ministry of Healthcare of the Russian Federation	1, Ul. Ostrovityanova, Moscow, Russia, 117997 Phone/Fax: [redacted]
5.	[redacted]	Federal State Budgetary Institution State Research Center for Dermatology, Venereology, and Cosmetology of the Ministry of Healthcare of the Russian Federation	3, bldg. 6 Ul. Korolenko, Moscow, Russia, 07076 Phone: [redacted]
6.	[redacted]	State Budgetary Educational Institution of Higher Professional Education Volgograd State Medical Academy of the Ministry of Healthcare and Social Development of the Russian Federation	1, Pl. Pavshykh Bortsov, Volgograd, Russia, 400131 Phone/Fax: [redacted]
7.	[redacted]	Limited Liability Company Institute for Medical Research	25A, Ul. Koli Tomchaka, St. Petersburg, Russia, 196084 Study site located at: 148, Moskovskiy Pr., St. Petersburg, Russia Phone: [redacted]

#	Principal Investigator (full name, and job title)	Name of study (clinical) site	Address and phone of study (clinical) site
8.	[redacted]	State Budgetary Institution I.I. Dzhanelidze St. Petersburg Research Institute for Emergency Care	3, Budapeshtskaya Ul., St. Petersburg, Russia, 192242 Phone/Fax: [redacted]
9.	[redacted]	State Healthcare Institution of Moscow Region Korolev Dermatology and Venereology Dispensary	48a, Ul. Gagarina, Korolev, Moscow Region, Russia, 141074 Phone: [redacted]
10.	[redacted]	State Budgetary Educational Institution of Higher Professional Education Irkutsk State Medical University of the Ministry of Healthcare and Social Development of the Russian Federation	1, Ul. Krasnogo Vosstaniya, Irkutsk, Russia, 664003 Phone: [redacted]
11.	[redacted]	Federal State Budgetary Military Educational Institution of Higher Professional Education S.M. Kirov Military Medical Academy of the Ministry of Defense of the Russian Federation	6 Zh, Ul. Akademika Lebedeva, St. Petersburg, Russia, 194044 Phone: [redacted]
12.	[redacted]	State Budgetary Institution of Ryazan Region Regional Clinical Dermatology and Venereology Dispensary	9, Ul. Sportivnaya, Ryazan, Russia, 390046 Phone: [redacted]
13.	[redacted]	St. Petersburg State Budgetary Healthcare Institution Dermatology and Venereology Dispensary No. 10 - Dermatology and Venereology Clinic, St. Petersburg, Russia	29A, Pr. Parkhomenko, St. Petersburg, Russia, 194021 Phone: [redacted]
14.	[redacted]	State Budgetary Educational Institution of Higher Professional Education Tver State Medical University of the Ministry of Healthcare of the Russian Federation	4, Ul. Sovetskaya, Tver, Russia, 170100 Phone: [redacted]
Medical institutions in Belarus			
1.	[redacted]	Educational Institution Vitebsk State Order of Peoples' Friendship Medical University" (study center located at: Health Institution Vitebsk Regional Clinical Center of Dermatology, Venereology and Cosmetology), Vitebsk, Belarus	27, Pr. Frunze, Vitebsk, Belarus, 210023 Site located at: 9, Ul. Bogdana Khmelnitskogo, Vitebsk, Belarus Phone/Fax: [redacted]

#	Principal Investigator (full name, and job title)	Name of study (clinical) site	Address and phone of study (clinical) site
2.	[redacted]	Healthcare Institution Mogilev Regional Dermatology and Venereology Dispensary	4, Ul. Sosnovaya, Mogilev, Belarus Phone/Fax: [redacted]
3.	[redacted]	Healthcare Institution Gomel Regional Clinical Dermatology and Venereology Dispensary	10, Ul. Meditsinskaya, Gomel, Belarus Phone/Fax: [redacted]

Name, job title, address and telephone number of the qualified physician responsible for taking medical decisions

Not applicable.

SYNOPSIS	
Protocol ID:	BCD-085-2
Study title	An International Multicenter, Randomized, Double-blind, Placebo-Controlled, Dose-finding Clinical Study of Efficacy and Safety of Subcutaneous BCD-085 in Patients with Moderate to Severe Plaque Psoriasis
Short title:	N/A
Study phase:	II
Study Sponsor:	JSC BIOCAD Mailing address: Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 Legal address: 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russian Federation, 198515
Test drug	BCD-085 (chemical name: monoclonal antibody selective for interleukin-17), solution for injection, [redacted] manufactured by JSC BIOCAD, Russia.
Placebo	[redacted], solution for injection (JSC BIOCAD, Russia). Manufacturer: JSC BIOCAD, Russia
Study purpose and objectives:	**Purpose:** To find an effective and safe dose of BCD-085 for multiple injections in patients with moderate to severe plaque-type psoriasis. **Study objectives:** 1. To determine the number of patients in each study arm who achieved PASI 75 at Week 12 of treatment. 2. To determine the number of patients in each study arm who achieved PASI 75 at weeks 4 and 8 of treatment. 3. To determine the number of patients in each study arm who achieved PASI 50/90 at weeks 4, 8, and 12 of treatment. 4. To evaluate the relative PASI improvement from baseline at weeks 4, 8, and 12, by study arms. 5. To evaluate the improvement from baseline in the body surface area (BSA) affected by psoriasis at weeks 4, 8, and 12, by study arms. 6. To evaluate the improvement from baseline in the nail psoriasis severity index (NAPSI) at weeks 4, 8, and 12, by study arms.

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	7. To determine the mean improvement from baseline in the intensity of pruritus measured by VAS (0-100 mm) at weeks 1, 4, 8, and 12, by study arms. 8. To evaluate the proportion of patients in each study arm who achieved sPGA score 0 or 1 at weeks 4, 8, and 12 relative to baseline. 9. To investigate patients' quality of life at weeks 4, 8, and 12 according to SF-36 and DLQI, by study arms. 10. To evaluate the proportion of patients in each study arm who develop adverse events with repeated administration of 40 mg, 80 mg, and 120 mg BCD-085 as compared to the placebo arm. [redacted]
Study design	This international multicenter study used a double-blind comparative design. The purpose of the study was to determine a therapeutically effective dose of BCD-085 to be repeatedly administered in patients with moderate to severe plaque-type psoriasis, as compared with placebo. The study is to include 120 adults who have moderate to severe plaque psoriasis stable for at least 6 months before inclusion in the study (i.e. there were no changes in morphological appearance, no severe aggravation or worsening of the disease occurred during this time, as judged by the investigator), 10% or greater body-surface area involvement, a psoriasis area and severity index (PASI) of 12 or more,[2] and a sPGA score of 3 or more.

[redacted]

[2] The severity of psoriasis must be confirmed by the investigator at screening.

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	Before being included in the study, patients must read and sign the informed consent form and undergo a screening examination (not longer than 4 calendar weeks) to confirm that they are eligible for the study. The Protocol does not stipulate any additional requirements for diet or physical activity during the screening or study periods. **Stratification and randomization** When all screening procedures are completed and the investigator approves patient's inclusion in the study, patients are stratified by body weight (≤80 kg / ≥81 kg), prior use of monoclonal antibodies for psoriasis (MAb-treated/ MAb-naive), current use of systemic non-biologics (yes/no), PASI score (< 20 / ≥ 20), signs of psoriatic arthritis (absent / present). After stratification, the patients are randomized 1:1:1:1 to one of four study arms: • **Arm 1:** patients received subcutaneous injections of 40 mg BCD-085 ([redacted]) once a week for the first 3 weeks (induction period) and then once every 2 weeks (maintenance period). For blinding purposes, these patients received two SC injections of placebo (1.0 mL each) together with each injection of BCD-085. Thus, the drug was administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period). • **Arm 2:** patients received 80 mg BCD-085 ([redacted]) once a week for the first 3 weeks (induction period) and then once every 2 weeks (maintenance period). For blinding purposes, these patients received one SC injection of placebo (1.0 mL) together with the injections of BCD-085. Thus, the drug was administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period). • **Arm 3:** patients received 120 mg BCD-085 ([redacted]) once a week for the first 3 weeks (induction period) and then once every 3 weeks (maintenance period). Thus, the drug was administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4,

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	Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period). • **Arm 4:** patients received placebo [redacted] SC injections on Day 1/Week 0, Day 1/Week 1, Day 1/Week 2, Day 1/Week 4, Day 1/Week 6, Day 1/Week 8, and Day 1/Week 10. Thus, the active period of the study involved the test drug/placebo injections weekly for the first three weeks of treatment and then once every 2 weeks. After assessment of the results at Week 12, all patients were transferred to a 4-week follow-up. During 14 weeks after the screening, 9 visits were performed to assess the efficacy, safety, [redacted] [redacted] **Study periods** • Screening (not more than 4 calendar weeks) • Therapy period: induction period and maintenance period: from Week 0 to Week 10 • Follow-up: 4 calendar weeks (through Week 14)
Study population	Males and females aged from 18 to 65 years, who had with stable moderate to severe plaque psoriasis and who did not respond to or were candidates for systemic therapy including TNF-α inhibitors or UV therapy.
Planned sample size	120 patients.
Inclusion criteria	1. Signed informed consent form 2. Age from 18 to 65 years old 3. Plaque-type psoriasis, moderate to severe, stable for at least 6 months at the time of inclusion in the study (i.e. no changes in the morphological signs of psoriasis, no significant worsening or exacerbations were seen during this period, as judged by the investigator)

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	4. Patients received at least one course of phototherapy or systemic therapy[3] for psoriasis or are candidates[4] for such treatment according to o the investigator 5. At screening, body surface area (BSA) affected by plague psoriasis of 10% or greater, PASI score of 12 or greater, and an sPGA score of 3 or greater 6. Treatment failure or unbearable toxicity with /contraindications for TNFα inhibitors or other biologics (monoclonal antibodies or their fragments) administered for at least 3 months. If such patient is included in the study, the treatment must be stopped at least 12 calendar days before signing the informed consent. 7. Laboratory values at screening: – Hemoglobin ≥ 9 g/dL (90 g/dL) – WBC ≥ 3 000/μL (3.0×10^9/L) – Platelets ≥ 100 000/μL (100×10^9/L) – Neutrophils ≥ 2 000/μL (2.0×10^9/L) – AST, ALT, and alkaline phosphatase ≤ 2.5 ULN – Serum creatinine < 176.8 μmol/L (2.0 mg/dL) – The negative test result for serologic and virologic markers for active/latent hepatitis B (HBV) and hepatitis C (HCV) 8. Negative pregnancy urine test in female subjects (no test is required in women who are post-menopausal for at least 2 years and in surgically sterile women) 9. No history of tuberculosis 10. Negative Diaskintest® results[5] or negative QuantiFERON test results[6] 11. Patients with uncertain Diaskintest® results were eligible for the study if they showed negative results with QuantiFERON test. Patients with uncertain QuantiFERON test were eligible for the study if a qualified specialist excluded TB infection (a written report had to be provided) and the chest X-ray exam performed

[3]Systemic therapy refers to any non-bioloogics (methotrexate, cyclosporine, acitretin, etc.), or biologics (TNF inhibitors, anticytokine drugs, anti-CD20 drugs, etc.)

[4]BCD-085 was planned to be used as either first- or second-line treatment as the study involved treatment-naive patients along with those who failed to respond to systemic or phototherapy.

[5]If the Diaskintest®/QuantiFERON test could not be performed, the Mantoux test was allowed instead. The patients with uncertain or positive Mantoux test results were allowed in the study if the following conditions were met: a qualified specialist excluded TB infection (a written report had to be provided) and the chest X-ray exam performed within 1 month before randomization revealed no signs of active TB infection.

[6]The QuantiFERON test was recommended if skin tests could not be performed (skin lesions in the middle of the inside forearm).

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	within 1 month before randomization revealed no signs of active TB infection 12. No history of or current alcohol or drug abuse at baseline 13. The patient had to be able to follow the Protocol procedures (in the investigator's opinion) 14. Patients of childbearing potential and their partners with preserved reproductive function had to consent to practice reliable contraceptive starting from 2 weeks before inclusion in the study and for 4 weeks after the last dose of screening to 4 weeks after the last dose of the study drug. This requirement does not apply to subjects who underwent surgical sterilization. Reliable contraception means one barrier method in combination with one of the following: spermicides or intrauterine device / oral contraceptives used by the subject's partner
Exclusion criteria	1. Baseline erythrodermic, pustular, and guttate psoriasis, drug-induced psoriasis, or any other skin diseases (e.g. eczema) that can affect/complicate the assessment of psoriasis treatment 2. Use of the following medications: – Prior use of monoclonal antibodies targeting IL17 or its receptor – Prior use of two or more TNFα-inhibiting monoclonal antibodies or their fragments – Prior use of two or more monoclonal antibodies against other targets – Prior use of monoclonal antibodies within 12 weeks before signing the informed consent – Oral glucocorticoids > 10 mg (equivalent to prednisolone) during 4 weeks prior to signing the informed consent and throughout entire screening period; oral glucocorticoids ≤ 10 mg/day if the dose was not stable for 4 weeks prior to signing the informed consent and through the entire screening period – Use of systemic non-biologics including methotrexate, sulfasalazine, cyclosporine, and acitretin within 4 weeks before randomization. This was an exclusion criterion if doses of said drugs were not stable for 4 weeks before signing the informed consent and during the entire screening period. If prior systemic therapy with non-biologics was stopped due to any reasons, the screening

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	period could be extended up to 8 weeks during which no new systemic non-biologics were allowed – Phototherapy (including selective UCB phototherapy and PUVA therapy) within 4 weeks before randomization – Live or attenuated vaccines administered at any time during 8 weeks before screening 3. Recurring, chromic or any other active infection if the investigator considers that the study drug can harm the patient 4. Documented HIV-infection or a history of a severe immunodeficiency of any origin 5. Positive screening results for Hbs-antigen, hepatitis B core antibodies (anti-HBc Ab)[7] and/or hepatitis C antibodies[8] 6. Current/history of tuberculosis 7. Current/history of herpes zoster[9] 8. Positive results of microprecipitation reaction together with positive TPHA assay results at screening 9. Concurrent diseases ongoing at screening that may increase the risk of adverse events during the study or affect the evaluation of psoriasis symptoms (mask, enhance or alter the symptoms of psoriasis, or cause clinical or laboratory signs/symptoms similar to those of psoriasis): – Active inflammatory diseases or aggravation of chronic inflammatory diseases other than psoriasis – Stable angina class III-IV, unstable angina or a history of myocardial infarction within 1 year before signing the informed consent – Cardiac failure moderate to severe (NYHA class III-IV) – Severe treatment-resistant hypertension[10]

Patients with positive anti-HBc Ab results are eligible for the study if all of the following conditions are met: negative qualitative PCR results for HBV DNA (this test is performed only if anti-HBV antibodies were detected); blood test results available for anti-HBc IgG and anti-HBC IgM; no abnormalities found in blood biochemistry; medical infections specialist provides a documented conclusion that the patient has no HBV; and the Sponsor approves enrollment of this particular patient.

Patients with positive anti-HBC Ab results are eligible for the study if all of the following conditions are met: negative qualitative PCR results for HCV DNA (this test is performed only if anti-HBC antibodies were detected); no abnormalities found in blood biochemistry; medical infections specialist provides a documented conclusion that the patient has no HCV; and the Sponsor approves enrollment of this particular patient.

[9] No additional test for antibodies to varicella-zoster virus was required. The decision was based on clinical signs and medical history.

Treatment-resistant arterial hypertension is defined as blood pressure above the target range despite the concurrent use of three anti hypertensive drugs of different classes, including a diuretic, and non-medication methods (salt-free diet, controlled physical exercise).

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	– A history of atopic asthma or angioedema – Moderate to severe respiratory failure, COPD grade 3/4 – Decompensated diabetes mellitus, decompensated hypothyroidism, decompensated hyperthyroidism – Systemic autoimmune diseases (including lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Crohn/s disease, ulcerative colitis, systemic sclerosis, inflammatory myopathies, mixed connective tissue disease[11], intersection syndrome, etc.) – Any other concurrent diseases (including but not limited to metabolic, hematologic, hepatic, renal, pulmonary, neurological, endocrine, cardiac, gastrointestinal, and infectious diseases) that may affect the course of psoriasis, affect the assessment of signs/symptoms of psoriasis, or put patients using the study treatment at additional risk 10. Malignancies within the past 5 years (other than adequately treated (cured) squamous or basal cell carcinoma, cervical cancer *in situ* or ductal carcinoma *in situ*) 11. Known severe allergies (anaphylaxis or multiple drug allergy) 12. Known allergy or intolerance to monoclonal antibody drugs (murine, chimeric, humanized, or human) or any other components of the study drug 13. Major surgery within 30 days before the screening, or a major surgery being scheduled at any time during the study 14. Severe infections (including those requiring hospitalization or parenteral antibacterial/antimycotic/antiprotozoal treatment) within 6 months before the first dose of the study drug 15. Systemic use of antibacterial/antimycotic/antiprotozoal drugs within 2 months before the first dose of the study drug 16. More than 4 episodes of respiratory infection within 6 months before screening 17. A history of epileptic attacks or seizures 18. The patient cannot stop phototherapy (including UVB and PUVA therapy) for psoriasis 19. Any concurrent diseases during which, in the investigator's opinion, the study treatment can harm the patient 20. Pregnancy, breastfeeding or planning for pregnancy while participating in the study

[11] Signs/symptoms of psoriatic arthritis were not considered an exclusion criterion.

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	21. Any psychiatric disorders, including a history of major depression and/or suicidal thoughts that can, in the investigator's opinion, put the patient at risk or affect patient's ability to follow the study protocol 22. Patients with the existence of or history of abuse of recreational drugs, prescription drugs, alcohol, or any other psychoactive substances 23. Participation in any other clinical trial within 3 months before screening or simultaneous participation in other clinical trials 24. Patients who were randomized to this study and then discontinued the study due to any reasons(i.e. patients who met all other inclusion/exclusion criteria), were not re-enrolled in this study
Study therapy	In this study, BCD-085 was administered to patients in three of four study arms. Patients received 40 mg, 80 mg, or 120 mg BCD-085 as SC injections according to the following schedule: once weekly for the first three weeks (induction regimen) and then once every two weeks (maintenance regimen). Thus, the drug was administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period). For blinding purposes, patients from 40 mg and 80 mg arms received [redacted] SC injection of placebo ([redacted]), respectively. Patients in the control arm received [redacted] SC injections of placebo ([redacted]). Placebo used in three arms had a similar composition that includes the excipients from the BCD-085 dosage form. Regardless of the arm to which the patient is assigned, injections will be performed by an authorized site medical nurse directly in the study site. Injections can be given to the abdomen, hips, or upper arms. Injections should be given at least 5 cm apart. During the entire study period, patients are not allowed to use phototherapy (UV-B), photochemotherapy (PUVA), biologics other than BCD-085, and live or attenuated vaccines. The patients were allowed to use systemic non-biologic therapies (methotrexate, sulfasalazine, chlorambucil, leflunomide, cyclosporine A, azathioprine, aromatic retinoids (acetretin), and glucocorticoids (> 10 mg of prednisolone equivalent per day) if their dose was stable for 4 weeks before signing the informed

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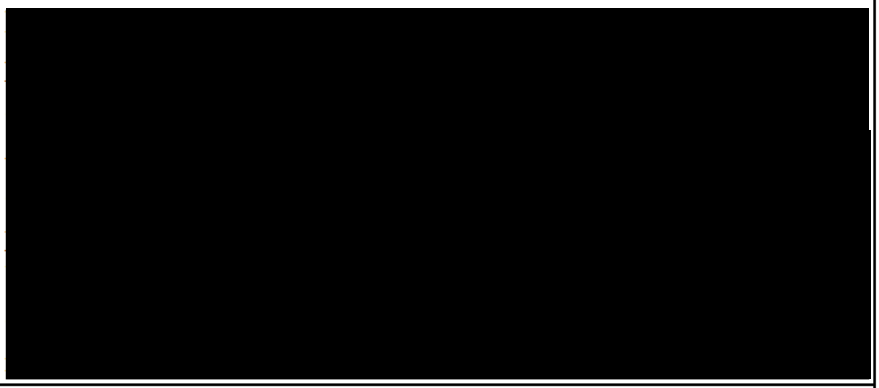
	consent and through the entire screening period). Patients were not allowed to change their systemic non-biologic treatment during the study, increase the dose, or add any new medications of this category. Discontinuation of systemic non-biologic therapies was allowed only if the patient had any life- or health-threatening adverse effects due to this treatment. Any modifications of the dosing regimen or dose reduction for systemic non-biologic therapy was allowed only after reconciliation with the Sponsor. The patients were allowed to use topical glucocorticoids on the face, underarm, and genitals. The patients could use topical moisturizing products, emollients, oils or salicylic acid-based products if necessary. The patients should discontinue all local skin products (medications or cosmetics) 24 hours before the planned PASI assessment.
Study procedures	To establish whether patients meet the inclusion/exclusion criteria and to assess the treatment efficacy (for enrolled subjects), patients will undergo, within the timeframes specified by the Protocol, a comprehensive medical exam including: • Taking baseline clinical characteristics and medical history • Physical examination • Measuring blood pressure and wrist pulse • Electrocardiography • Chest X-ray / fluorography (front view) • Blood hematology • Blood biochemistry • Pregnancy test[12] • Assessment of the patient's infection status (Diaskintest® or blood testing for interferon gamma (QuantiFERON test)); if these tests are impossible to perform, the Mantoux test can be done and the patient can be examined by the TB specialist (required if the Diaskintest® and QuantiFERON test results are uncertain or if the Mantoux results are uncertain or positive), anti-HIV antibodies [HIVAg/Ab Combo], HBs-antigen, anti-HBcor antibodies [IgG + IgM/ IgG/ IgM], and anti-HCV antibodies [IgG + IgM], qualitative PCR for HCV RNA / HBV DNA (only if the patient was positive for respective antibodies), consultation with an infectious disease specialist (required only if the

[12] Pregnancy test is required only for women of childbearing potential and does not apply to post-menopausal women.

SYNOPSIS	
	patient is positive for anti-HBcor antibodies or anti-HCV antibodies), microprecioitation reaction, and a direct hemagglutination assay (T. pallidum) • Calculation of the body surface area affected by psoriasis (BSA) • Assessment of the extent and severity of psoriasis with PASI • Assessment of psoriasis involvement of nails (NAPSI) • Assessment of psoriasis severity with sPGA[13] • The severity of pruritus assessed with the visual analog scale (0-100 mm) • DLQI and SF-36 questionnaires To measure the efficacy of treatment in the timeframes specified by the Protocol, the changes over time in the PASI, NAPSI, and sPGA scores, VAS scores for pruritus intensity, and the quality of life (DLQI and SF-36 scores) will be evaluated. To visualize the efficacy measures during the study, patients will be photographs were taken from each patient on PASI assessment visits. For safety evaluation, the following will be closely monitored: all general disorders (including fever and flu-like symptoms), abnormal physical signs (BP, wrist pulse), infections, abnormalities in certain laboratory values (CBC results: hemoglobin, RBC, platelets, WBC including changes in the WBC differential, ESR; blood biochemistry: glucose, total bilirubin, indirect bilirubin, ALT, AST, GGT, LDH, total protein, creatinine, urinalysis; coagulation profile: prothrombin ratio, APTT), cardiac disorders (ECG), lung abnormalities (chest X-ray / fluorography). 
Total study duration	The expected duration of the study is 26 months, which includes patients' recruitment (up to 12 months), treatment period, follow-up period, and data collection and statistical processing. The

[13]Static Physicians Global Assessment

SYNOPSIS	
	maximum expected the duration of each subject's participation is 18 weeks including the screening (up to 4 weeks), treatment (10 weeks) and follow-up (4 weeks).
Efficacy assessment	**Primary endpoint:** • The proportion of patients in each study arm who achieved a PASI 75 at Week 12 of treatment **Secondary endpoints:** • The proportion of patients in each study arm who achieved a PASI 75 at weeks 4 and 8 of treatment • The proportion of patients in each study arm who achieved a PASI 50/90 at weeks 4, 8, and 12 of treatment • The relative PASI improvement from baseline in each study arm at weeks 4, 8, and 12 • The relative BSA improvement from baseline in each study arm at weeks 4, 8, and 12 • The relative NAPSI improvement from baseline in each study arm at weeks 4, 8, and 12 • The mean change from baseline in the intensity of pruritus measured by VAS (0-100 mm) in each study arm at weeks 1, 4, 8, and 12 • The proportion of patients in each study arm who achieved an sPGA score 0 or 1 at weeks 4, 8, and 12 relative to baseline • The mean change from baseline in the QoL score in each study arm (assessed using the DLQI and SF-36 scales) at weeks 4, 8, and 12
Safety assessment	**Secondary endpoints:** • The proportion of patients who developed SAEs • The proportion of patients who developed AEs • The proportion of patients who developed administration site reactions • The proportion of patients who developed grade 3/4 AEs/SAEs • The proportion of patients who discontinued the study due to AEs/SAEs
[redacted]	[redacted]

SYNOPSIS

SYNOPSIS	
	[redacted]
[redacted]	[redacted]
Statistical analysis	**Methods of analysis** Statistical analysis will be performed by using R environment and STATISTICA 10 package. To compare normally distributed data, it is planned to use the following tests: two-sample Student t-test and ANOVA. For non-normally distributed data, it is planned to use Mann-Whitney test and ANOVA. The regression analysis will be used for quantitative efficacy data. The categorical data will be processed using the Fisher's exact test, Yates-corrected χ^2 test, and Cochran-Mantel-Haenszel test. **Safety assessment** The safety analysis will include all patients who received at least one dose of the investigational product. Additionally, the SAE analysis will include all randomized patients starting from the ICF signing and until the end of their participation in the study. **Efficacy analysis** Per protocol, the efficacy analysis was planned to include all patients who received at least one dose of BCD-085/placebo and who attended at least one visit next visit. If no data were available at Week 12, the data from the last assessment were to be used (last-observation-carried-forward method). In addition, these cases had to be considered non-responders and analyzed separately. [redacted]

SYNOPSIS	
	[redacted] **Report preparation** **Final report** The final report will contain results of the PK, safety, and efficacy endpoint analysis for the BCD-085 doses after a 14-week observation for 120 patients.

1. STUDY JUSTIFICATION

1.1. Introduction

1.1.1. Overview of disease pathogenesis, epidemiology, and currently available treatment options

1.1.1.1. Epidemiology and significance of the disease

Psoriasis is a common skin disease. In developed countries, up to 2% to 3% of the population has this disease. In Russia, about 100 000 new cases are registered per year, with the prevalence of psoriasis being about 1%.

Clinical signs of psoriasis may differ by their severity, varying from mild forms manifesting as a few local lesions (rashes) on the skin to severe forms (about 30% of cases) affecting a significant percentage of the body surface.

In the recent decades, severe therapy-resistant forms of psoriasis have become more common, which significantly affect the patients' quality of life and lead, in some cases, to disability. This determines the social significance of psoriasis. According to Krueger et al., psoriasis, as a medical and social problem and a factor reducing the quality of life, shares the first place with depression, cardiovascular disorders, and diabetes.

Today, psoriasis is considered incurable. However, modern treatment options are able to significantly improve the clinical course of the disease and make remissions longer.

1.1.1.2. Current treatment options

Psoriasis is commonly treated with topical agents such as glucocorticoids, calcipotriol, anthralin, coal tar extracts, etc. These treatment options are indicated in patients with mild psoriasis.

Today, phototherapy is an important option in the treatment of psoriasis: photochemotherapy (PUVA) is a combination of the UVA light and a photosensitizing agent taken orally; selective phototherapy, which is a combination of middle- and long-wave UV light; and the narrowband UVB therapy. The light is likely to exert its therapeutic effects by stimulating the production of cytokines with immunosuppressive effects, enhancing the expression of several molecules on the cell surface, and inducing apoptosis.

Retinoids (synthetic derivatives of vitamin A) have been used in psoriasis for more than 25 years. Retinoids inhibit the proliferation of epidermis, normalize keratinization, exert immunomodulating effects on dermal cells, and stabilize membrane structures of cells.

In the recent decades, opinions about mechanisms of psoriasis have changed, and now it is considered a systemic autoimmune disease. Thus, approaches to its therapy have been revised as well. Cytostatic agents (methotrexate), systemic glucocorticoids, and cyclosporine for the treatment of moderate to severe psoriasis are taking a backseat to agents that are more selective.

Biological medicinal products became a major achievement in the treatment of patients with psoriasis. Introducing the biologics into clinical practice was a breakthrough in the therapy of this disease and changed the world opinion about its potential outcomes. All biologics approved for the treatment of psoriasis show high effectiveness as compared to conventional medications. Due to their high specificity, monoclonal antibodies are low-toxic and produce minimum adverse effects.

Biologics used in clinical practice can be classified as follows [1]:

- Modulators of T-cells (alefacept)
- Ihibitors of timor necrosis factor alpha (adalimumab, certolizumab, etanercept, golimumab, and infliximab)
- Inhibitors of interleukins 12 and 23 (ustekinumab).

The first biologics approved by the FDA for the treatment of psoriasis were alefacept (anti-CD2) and efalizumab (anti-CD11). Efalizumab was also approved by the EMA. In 2009, efalizumab was recalled from the market following several cases of multifocal leukoencephalopathy reported with a long-term use of the drug.

TNF-α inhibitors are monoclonal antibodies that with high affinity and specificity bind to the TNF-α thus preventing it from interaction with the receptors and inducing the lysis of TNF-α expressing cells in the presence of the complement. Today, these products are well investigated and have firmly established themselves as treatments for psoriasis.

Another MAb commonly used in psoriasis is ustekinumab, which has a different mechanism of action. Ustekinumab contains fully human MAbs to the p-40 subunit of both IL-12 and IL-23. These cytokines play a key role in the pathogenesis of inflammation mediated by the T-helper cells 1 and 17 [1].

Thus, psoriasis is a common and socially significant disease. The most effective treatments for psoriasis are biologics that affect various components of the disease. The recent findings suggest that interleukin-17 pays a key role in the development of psoriasis. Several drugs blocking

this cytokine demonstrated high efficacy and favorable safety in a number of clinical studies. Thus, development of drugs that block IL-17 signaling is a promising approach in searching new highly effective and safe treatments for psoriasis.

1.1.2. Background information for studied therapy

[redacted]

[redacted] [10].

[redacted] [26, 27, 28], [redacted], 24, 25],

[redacted]

[redacted] [11, 12, 13, 14].

[redacted]

[redacted]

[redacted]

1.2. Name and description of investigational products

Investigational products in this study include BCD-085 (test drug) and placebo.

Test drug:

Invented name: N/A

Internal code: BCD-085

Chemical name: anti-IL-17 monoclonal antibody

BCD-085, a therapeutic monoclonal antibody selective for interleukin-17, which has been developed by JSC BIOCAD, is an innovative biotechnology product. Its physicochemical, biological, and toxicological properties have been characterized in a number of non-clinical studies. BCD-085 has been shown to bind interleukin-17 with the affinity [redacted] Phase I clinical study in healthy volunteers assessed the pharmacokinetics of BCD-085 and confirmed its safety upon a single SC

injection of ascending doses (refer to section 1.3.2), proving the feasibility of its further clinical investigation.

If the clinical development is successful, implementation of a Russian innovative monoclonal anti-IL-17 antibody into clinical practice will improve the therapy of a wide range of autoimmune disorders and other chronic inflammatory diseases.

1.3. Relevant non-clinical and clinical aspects

1.3.1. Non-clinical studies

1.3.1.1. Study of physicochemical properties and potency

Physicochemical studies have shown that BCD-085 possesses the following characteristics:

- ✓ The anti-IL-17 monoclonal antibody in BCD-085 binds human interleukin-17 with affinity [redacted]
- ✓ The anti-IL-17 monoclonal antibody selectively blocks the production [redacted]
- ✓ The purity characteristics of the anti-IL-17 monoclonal antibody allow using it as a study drug in clinical studies in humans.

1.3.1.2. Non-clinical pharmacodynamics

1.3.1.2.1. Investigation of BCD-085 potency in the model autoimmune encephalitis

[redacted]

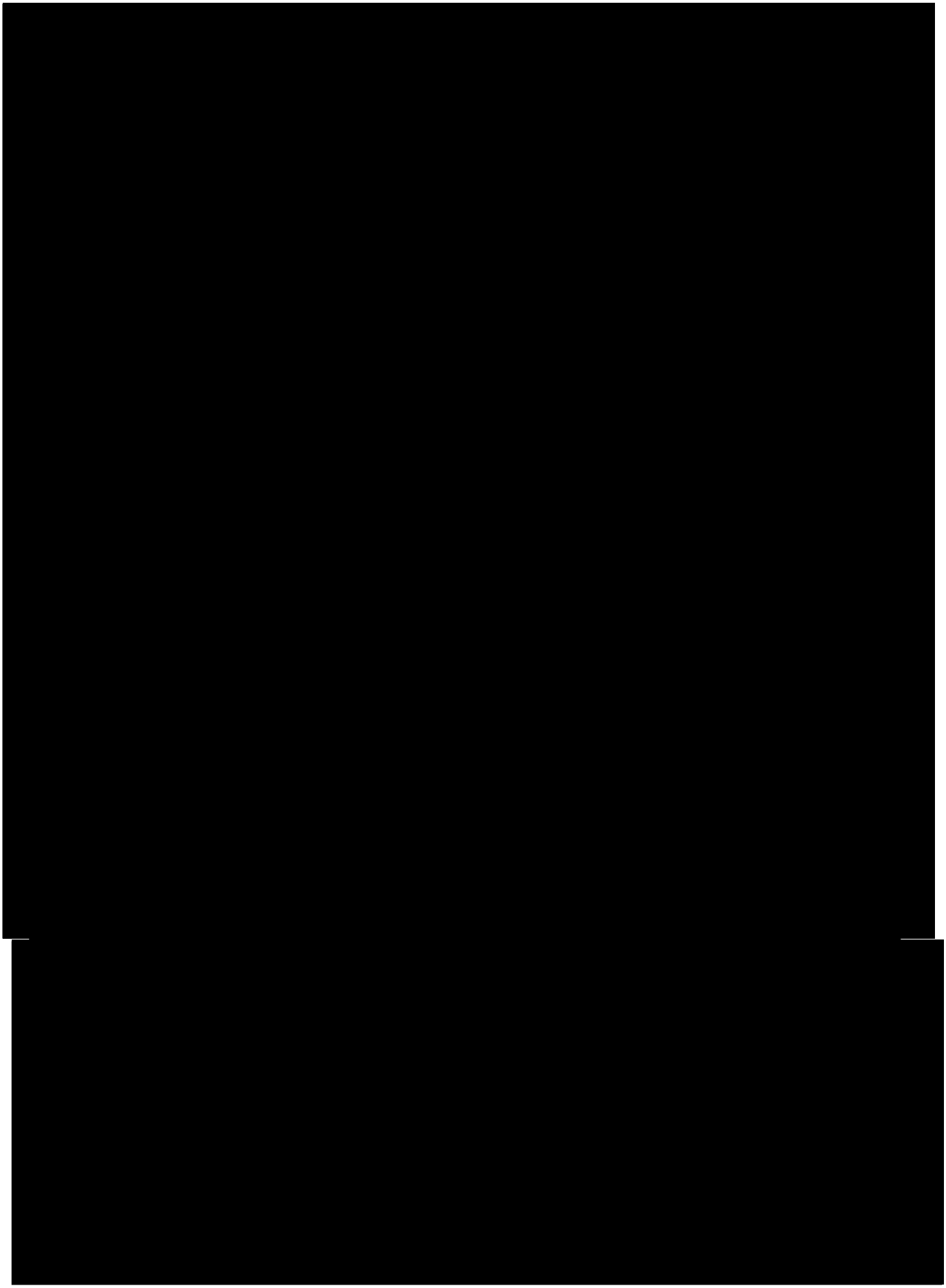
[redacted]

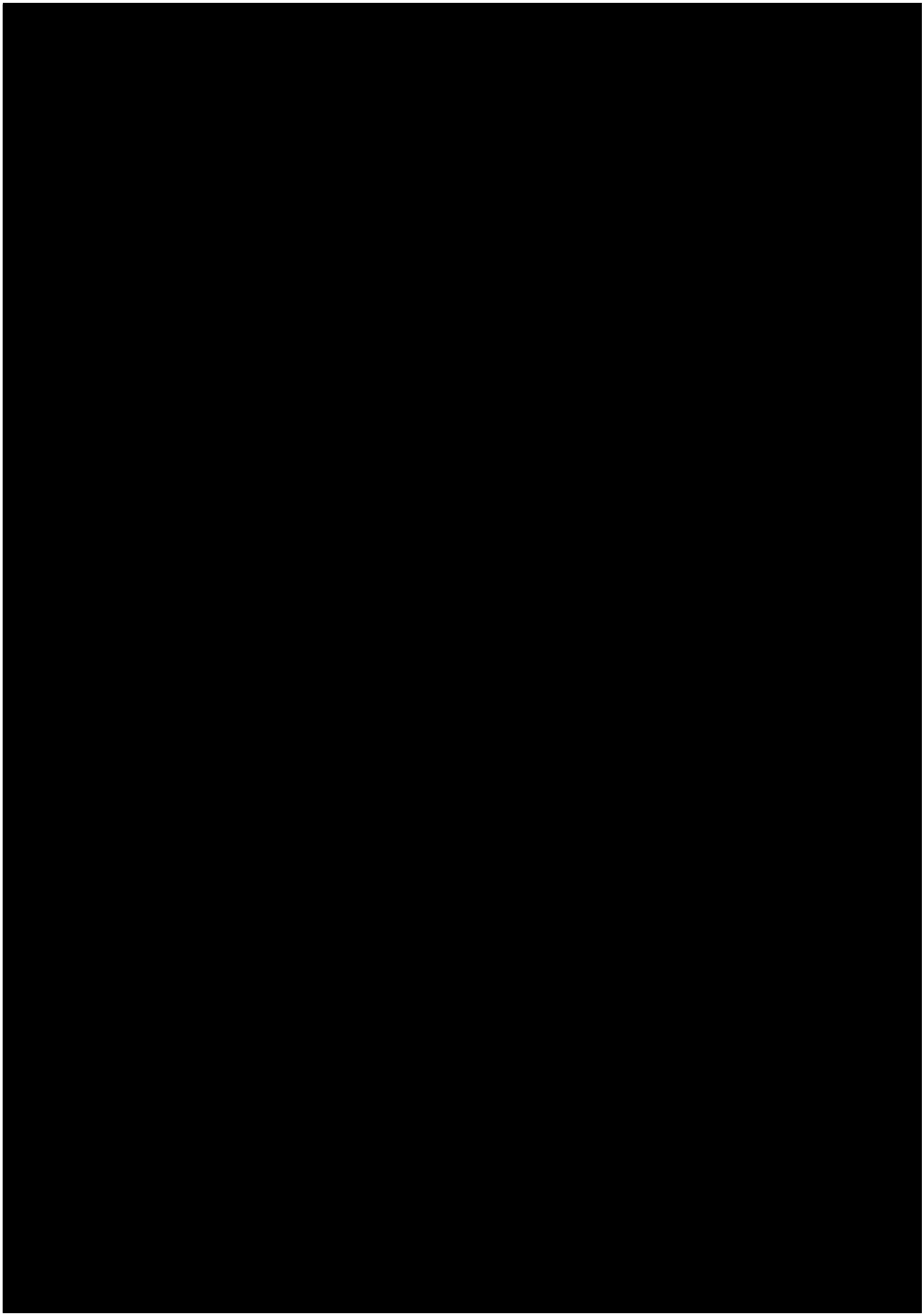
[redacted]

1.3.1.2.2. Investigation of BCD-085 potency in the model collagen-induced arthritis

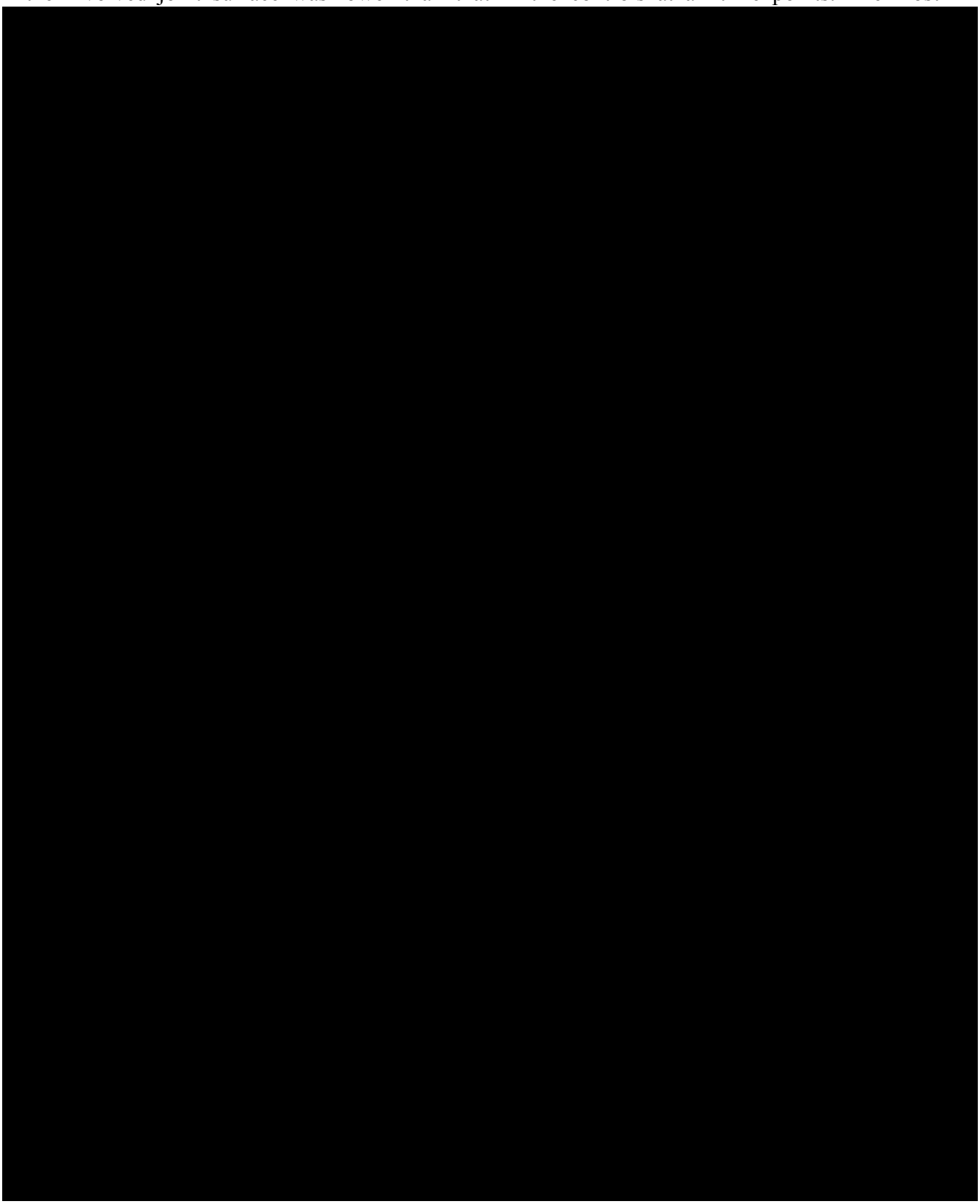
The pharmacodynamics of the anti-IL-17 monoclonal antibody was studied in the model collagen-induced arthritis in cynomolgus monkeys (*Macaca fascicularis*). The drug was given as multiple SC injections. The drug was administered at a dose of 4.0 mg/kg (4 animals) and 8.0 mg/kg (4 animals) once a week for 4 weeks following the second injection of collagen used to induce arthritis. Equal volumes of normal saline were used as a negative control (4 animals).

[redacted]





The inflammatory reaction evaluated by the involved joint surface was the most severe in animals from the placebo group (controls). In all groups that received BCD-085, the percentage of the involved joint surface was lower than that in the controls at all time points. The most



1.3.1.2.3. Repeated-dose immunogenicity study of BCD-085

Immunogenicity of BCD-085 was studied in healthy cynomolgus monkeys (*Macaca fascicularis*) after multiple SC injections at a dose of [redacted] The drug was injected twice within 1 month followed by a 2-week recovery period. In parallel with the BCD-085 concentration assay, blood samples were drawn for immunogenicity testing.

Analysis of the presence/absence of binding anti-BCD-085 antibodies (the number of animals positive for binding antibodies) and the titer of binding antibodies upon repeated (given twice) SC injections has demonstrated that animals did not develop immunoglobulins binding BCD-085. The concentration of anti-BCD-085 antibodies was below the lower limit of detection. Thus, all animals were considered negative for binding anti-BCD-085 antibodies. Based on the experimental findings, we can conclude that BCD-085 is non-immunogenic when used according to the studied regimen.

The study has shown that two SC injections of [redacted] BCD-085 are non-immunogenic in cynomolgus monkeys (do not result in accumulation of anti-BCD-085 binding antibodies).

1.3.1.2.4. Single-dose toxicity of BCD-085

The single-dose toxicity of SC anti-IL-17 monoclonal antibody (BCD-085) was studied at doses: [redacted]. The minimum dose used in this study is equivalent to the expected therapeutic dose in humans with an account of the interspecies dose conversion factor. The medium dose was equivalent to 5 expected therapeutic doses. The maximum dose was equivalent to 10 expected therapeutic doses.

The study used 16 male and female monkeys (*Macaca fascicularis*) with body weight from 3.0 kg to 7.0 kg:

1. BCD-085 [redacted] (2 males and 2 females)
2. BCD-085 [redacted] (2 males and 2 females)
3. BCD-085 [redacted] (2 males and 2 females)
4. Control (placebo): 2 females and 2 males.

No animals died during the experiment and no animals developed any clinical signs of toxicity. No animals had any of the following:

- Changes in appetite
- Altered breathing pattern
- Changes in stool

- Changes in vegetative reactions (pupil diameter, eye slit size, salivation, involuntary defecation, urination, increased diuresis) were observed
- Effects on the pelage (piloerection, alopecia, pelage color)
- Eye changes (tearing, discharge)
- Effects on animal behavior.

The study results showed that BCD-085 in the tested doses does not cause animal death or clinical signs of toxicity. It was technically impossible to inject the doses needed to assess the lethal dose (due to the limitations on the volume that can be injected). The general health of animals was satisfactory throughout the entire experiment; no body weight loss was registered. CBC parameters and blood biochemistry markers of the liver and urinary system health did not change during the observation period and were within the normal ranges.

Some decrease in the serum glucose level was observed with the medium [redacted] and maximum [redacted] doses of BCD-085. This trend was observed on Day 7 and reached its maximum on Day 14 of the experiment (end of the experiment). At the end of the experiment, the serum glucose in animals dosed with [redacted] and [redacted] BCD-085 reached the lower level of normal. These findings suggest that the treatment with BCD-085 may be associated with disturbances of carbohydrate metabolism.

1.3.1.2.5. Repeated-dose toxicity of BCD-085

Repeated-dose toxicity was investigated in 18 monkeys (*Macaca fascicularis*). Three doses of BCD-085 were used: the maximum dose was two-fold higher than the MTD (determined in the single-dose toxicity study) - [redacted].

Animals were distributed into 4 groups (by investigational product and its dose):

Group 1 - BCD-085 [redacted] (2 females and 2 males).

Group 2 - BCD-085 [redacted] (2 females and 2 males).

Group 3 - BCD-085 [redacted] (3 females and 3 males).

Group 4 - placebo controls (2 females and 2 males).

The study drug was administered as SC injections of the freshly prepared solution in 0.9% sodium chloride. The drug was administered once a week for 4 weeks.

No deaths were recorded throughout the study. No clinical signs of toxicity were seen upon repeated injections of [redacted] BCD-085:

- No changes in the appetite
- No altered breathing pattern

- No stool changes
- No changes in autonomic reactions (pupil diameter, eye slit size, salivation, involuntary defecation, urination, increased diuresis
- No changes of the pelage (piloerection, alopecia, pelage color)
- No eye changes (tearing, discharge)
- And no changes in the behavior of cynomolgus monkeys.

The test animals tolerated the drug well. They developed no clinical signs of toxicity, no motor or behavioral disturbances, no thermogenic reactions, and no changes were observed in how animals interacted with investigators. These findings were true for all tested doses and did not depend on the gender of animals. In this experiment, [redacted] BCD-085 did not affect the body weight of the monkeys. Multiple (once weekly for 4 weeks) SC injections of BCD-085 at the highest dose [redacted] was associated with e tendency towards decreased body weight of cynomolgus monkeys. By the end of the drug-free recovery period, the body weight was back to baseline values.

Repeated SC injections of the medium [redacted] and maximum [redacted] doses did not affect the CBC parameters assessed in this study. Injections of [redacted] BCD-085 were associated with a reversible increase in the ESR observed at the end of the injection period (Week 4).

The therapeutic anti-IL-17 monoclonal antibody (JSC BIOCAD) in all tested doses did not affect the hemostasis, protein synthetic function of the liver, and lipid metabolism; it does not elevate concentrations of enzymes specific for liver damage. It has been shown that repeated administration of [redacted] BCD-085 to *Macaca fascicularis* decreases the serum glucose level; therefore, the drug potentially can affect the carbohydrate metabolism.

In this experiment, no drug effects were observed on the CNS, bioelectric activity of the heart, or urinary function (regardless of the dose).

In non-clinical investigations, animals tolerated BCD-085 well. The drug did not alter the cardiovascular and urinary function and did not produce any local irritative effects. **The drug is considered low-toxic and can be recommended for clinical development.**

1.3.1.2.5. Local tolerance studied as part of the BCD-085 repeated-dose toxicity

Local tolerance was evaluated by external examination and histological findings. Tissues at the injection site and regional lymph nodes were taken for histology.

The study results prove that BCD-085 (JSC BIOCAD) exerts no local irritative effect when injected subcutaneously. Histologic studies did not show any changes in the injection sites or draining lymph nodes.

1.3.1.2.6. Immunotoxicity of BCD-085

Immunotoxicity upon multiple SC injections of BCD-085 was studied for the following doses: [redacted]. The experiment was conducted in 9 male monkeys (*Macaca fascicularis*) of 3.0 kg to 7.0 kg. Animals were divided into three groups depending on the dose/drug administered:

1. BCD-085 [redacted] (3 males)
2. BCD-085 [redacted] (3 males)
3. Placebo controls (3 males).

The assessment of the lymphocyte phenotypes in the peripheral blood of primates upon repeated injections of BCD-085 has shown that the test drug does not alter the subpopulation ratio.

Assessment of drug effects on humoral immunity is one of the main parts of immunotoxicity study.

The obtained results evidence that repeated SC administration of BCD-085 does not alter the levels and balance of immunoglobulins *M, G, A, and E*.

No changes in the phagocytic activity were observed during the study. Its intensity was similar in animals dosed with BCD-085 and controls.

No significant changes in the intensity of lymphocyte proliferation were observed throughout the experiment, regardless of the BCD-085 dose. Proliferation activity in the groups of primates treated with BCD-085 was similar to that in the placebo controls.

Experimental findings suggest that repeated administration of BCD-085 was not associated with significant changes in any variables assessed in this study. Thus, it was considered that multiple SC administration of [redacted] BCD-085 in cynomolgus monkeys produces no immunotoxicity in the said experimental settings.

[redacted]

1.3.1.2.8. Allergy-inducing potential of BCD-085

[redacted]

[redacted] Therefore, BCD-085 did not have any allergenic potential. These results confirm the feasibility of using BCD-085 in clinical development.

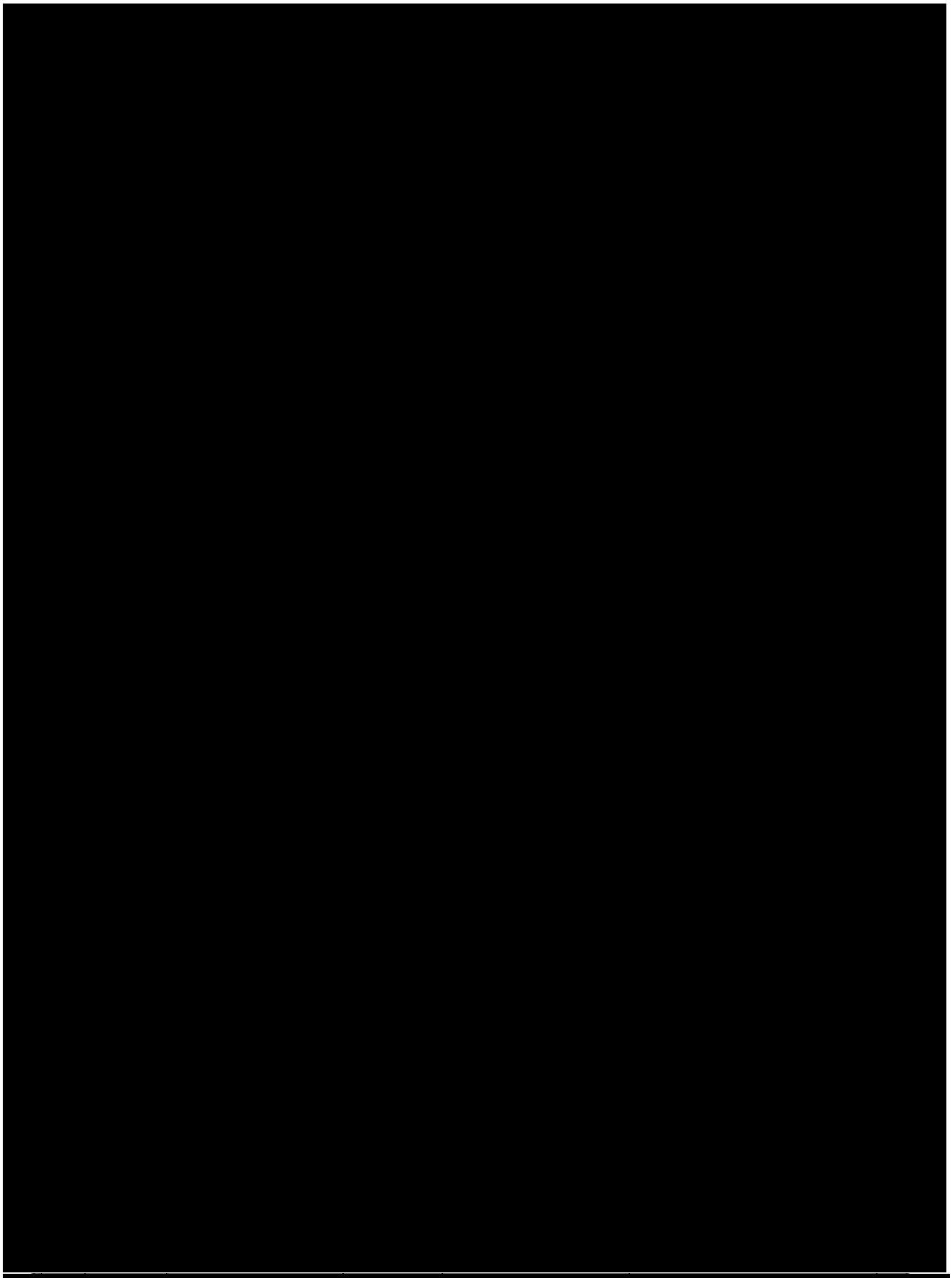
[redacted]

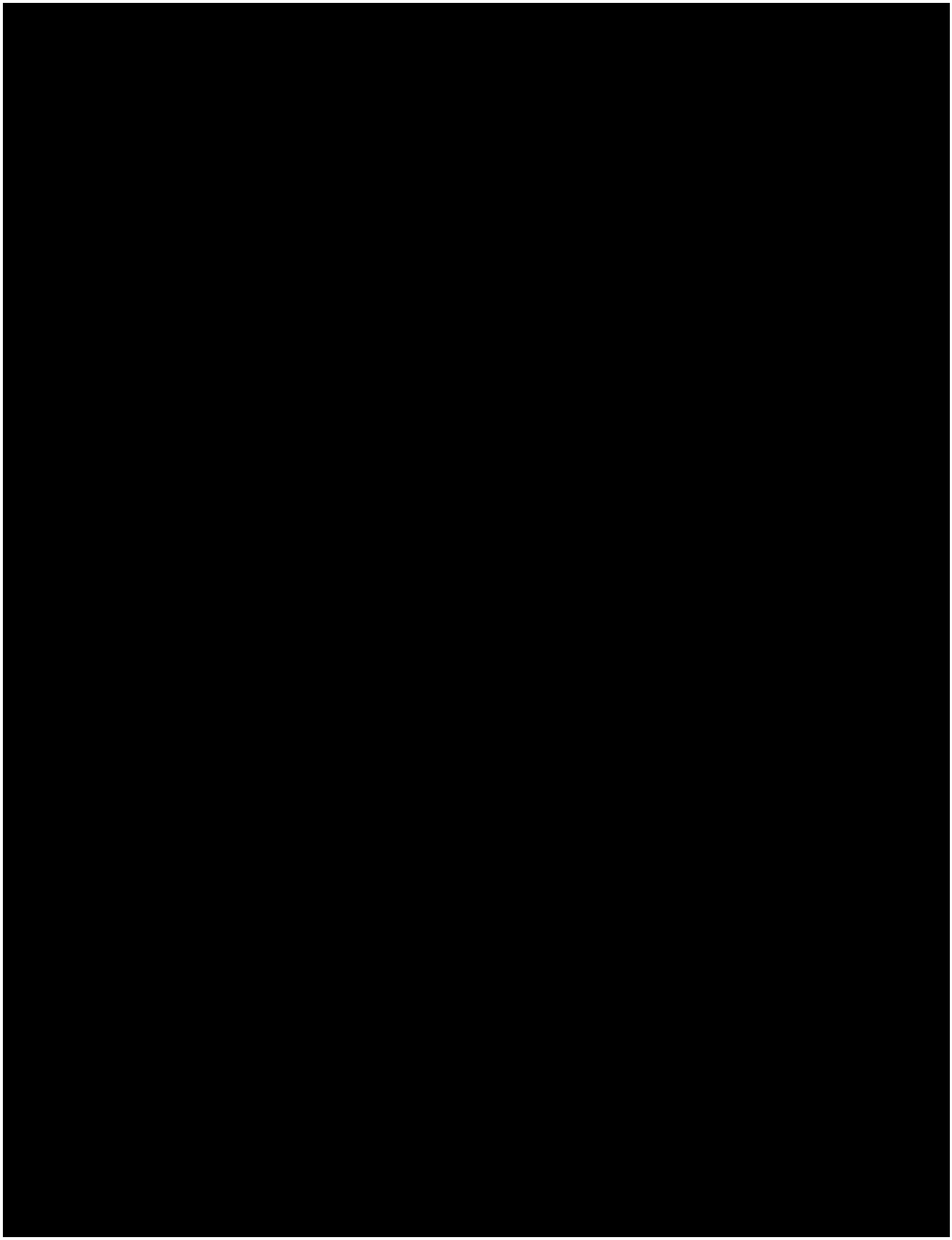
[redacted]

1.3.1.2.10. Cross-reactivity of BCD-085

The study aimed at evaluating the cross-reactivity of BCD-085 by immunohistochemical (IHC) staining in frozen normal human tissues.

The frozen normal human tissues consisted of autopsy material. Thirty-three types of human tissue were used for analysis, [redacted]





1.3.2. Clinical trials

By the time this Protocol was written, phase I clinical study was completed that investigated the safety, tolerability, and pharmacokinetics of single ascending doses of BCD-085. Results of this study are described below.

1.3.2.1. Comparative single-dose study of pharmacokinetics, safety, and tolerability

When this Protocol was prepared, an open-label clinical study of the pharmacokinetics, tolerability, and safety of single ascending doses of BCD-085 in healthy volunteers was completed. This study demonstrated a favorable safety profile of the drug and allowed characterizing the pharmacokinetics of BCD-085.

According to the approved protocol, this clinical study of the safety, tolerability, and PK of single ascending doses of BCD-085 had to include 8 cohorts of healthy male volunteers. Participants were included in the study as follows:

1. Cohort 1: 1 volunteer who received a single SC injection of BCD-085 at a dose of 0.05 mg/kg of body weight.
2. Cohort 02: 3 volunteers who received a single SC injection of BCD-085 at a dose of 0.05 mg/kg of body weight.

3. Cohort 03: 3 volunteers who received a single SC injection of BCD-085 at a dose of 0.25 mg/kg of body weight.

4. Cohort 04: 3 volunteers who received a single SC injection of BCD-085 at a dose of 0.825 mg/kg of body weight.

5. Cohort 05: 3 volunteers who received a single SC injection of BCD-085 at a dose of 1.25 mg/kg of body weight.

6. Cohort 06: 3 volunteers who received a single SC injection of BCD-085 at a dose of 1.75 mg/kg of body weight.

7. Cohort 07: 3 volunteers who received a single SC injection of BCD-085 at a dose of 2.25 mg/kg of body weight.

8. Cohort 08: 3 volunteers who received a single SC injection of BCD-085 at a dose of 3.00 mg/kg of body weight.

Volunteers were included in the study one after another. At first, 1 volunteer was included in Cohort 01 and receives a single subcutaneous injection of BCD-085 at a dose of 0.05 mg/kg (estimated starting safe dose). If the patient had no grade 3/4 toxicity events related to the drug within the first 7 days after the injection, 3 more volunteers were included in Cohort 02, etc.

No events of dose-limiting toxicity (DLTs) were observed, and 22 male volunteers were included in the study. Each participant had a verified diagnosis “healthy” according to the results of the standard clinical, laboratory, and instrumental examinations.

The study drug was well tolerated. Most adverse events were laboratory abnormalities (of blood hematology and biochemistry), of grade 1 severity, and, according to investigators, possibly related to the study therapy. No injection site reactions were reported. No dose-limiting toxicity was reported.

Hepatobiliary disorders were the most common AEs. They included elevated AST (1 event in cohorts 05 and 06) and elevated ALT (1 event in cohorts 01 and 05), which were recorded in 9.09% of subjects. Blood and lymphatic system disorders were reported less frequently and were represented by 1 case of neutropenia in Cohort 05 (4.54%). The overall number of AEs was 6 (27.27%), including 5 (22.73%) that did not meet the seriousness criteria. All AEs (except for SAEs) were of severity grade 1 and considered related to the study treatment. The investigators judged the causality as possible.

One SAE was reported in the study – a closed head injury (concussion of the brain) that occurred in a road accident. The SAE was not related to the study drug. The investigator qualified this SAE as grade 3.

No deaths were reported in the study.

Table 4. Cumulative frequency of AEs by cohort (n = 22) (the Table displays only the cohorts where at least 1 AE was registered. Cohort 01 - 0.05 mg/kg, Cohort 03 - 0.25 mg/kg, Cohort 05 - 1.25 mg/kg, Cohort 06 - 1.75 mg/kg).

AE	Cohort			
	01 (n=1)	03 (n=3)	05 (n=3)	06 (n=3)
	n (%)	n (%)	n (%)	n (%)
ALT increased (grade 1)	1 (100%)	-	1 (33.3%)	-
AST increased (grade 1)	-	-	1 (33.3%)	1 (33.3%)
Neutropenia (grade 1)	-	-	1 (33.3%)	-
Closed head injury Brain concussion (grade 3)	-	1 (33.3%)	-	-

The PK study was conducted in all 8 cohorts and included standard PK parameters that allow describing the distribution and elimination of the study drug from the body after a single-dose administration:

- $AUC_{0\text{-}1344}$ (area under the *time-concentration* curve from administration to 1344 h [57 days post-dosing])
- $AUC_{0\text{-}\infty}$ (from administration to infinity)
- C_{max} – maximum serum concentration of anti-IL17 antibody
- T_{max} - time to C_{max}
- $T_{½}$ - elimination half-life
- K_{el} - elimination constant
- CL - total clearance

In addition, the mean residence time (MRT) and the area under the first moment curve (AUMC) were calculated.

Concentrations of BCD-085 increased in a direct proportion to the dose and achieved their maximum in 55 to 211 hours (on an average, in 168 h, i.e. by the end of the first week of the follow-up), then decreasing gradually. The elimination half-life did not depend on the dose and was typical for monoclonal antibodies (15-22 days).

Figure 3. Summarized results for the AUC_{0-1344} and $AUC_{0-\infty}$ by cohorts. The Y axis represents the AUC ng/mL×h; the X axis represents the cohorts: Cohort 01 - 0.05 mg/kg, Cohort 02 - 0.05 mg/kg, Cohort 03 - 0.25 mg/kg, Cohort 04 - 0.825 mg/kg, Cohort 05 - 1.25 mg/kg, Cohort 06 - 1.75 mg/kg, Cohort 07 - 2.25 mg/kg, and Cohort 08 - 3.0 mg/kg).

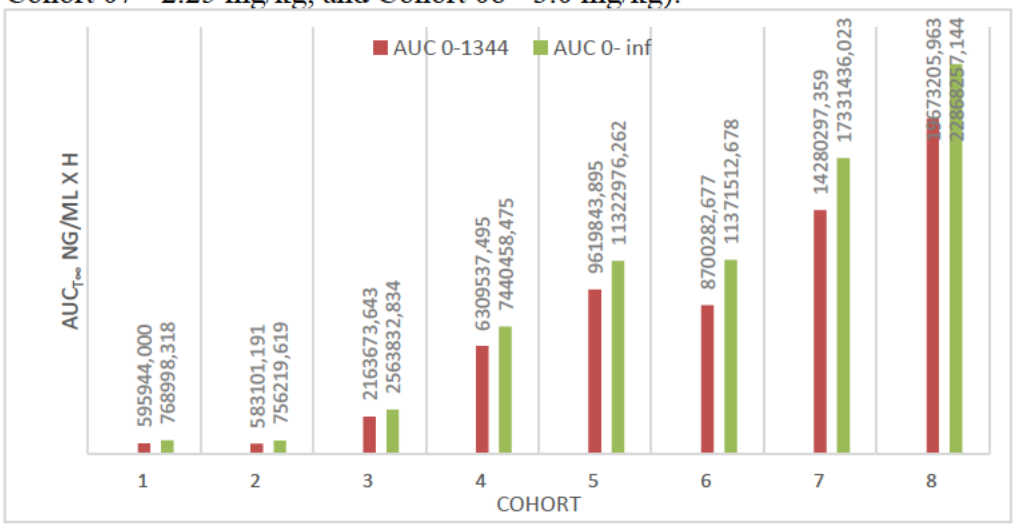
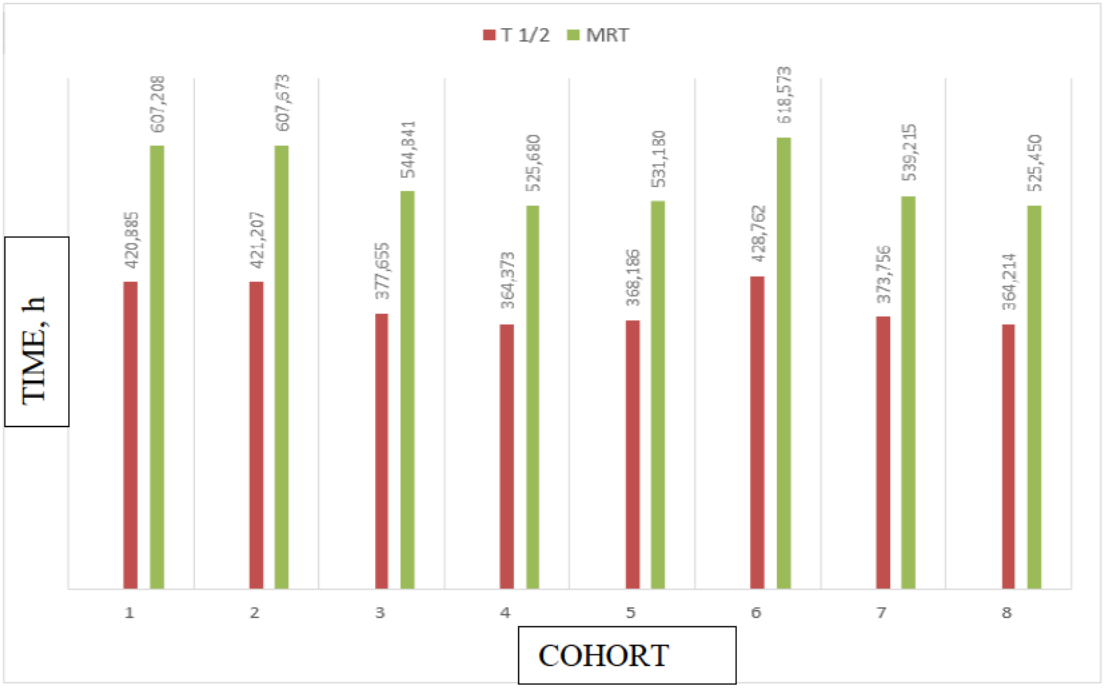


Figure 4. Summarized results for the elimination half-life and MRT of BCD-085 in the serum of healthy volunteers, by cohorts. The Y axis represents the AUC ng/mL×h; the X axis represents the cohorts: Cohort 01 - 0.05 mg/kg, Cohort 02 - 0.05 mg/kg, Cohort 03 - 0.25 mg/kg, Cohort 04 - 0.825 mg/kg, Cohort 05 - 1.25 mg/kg, Cohort 06 - 1.75 mg/kg, Cohort 07 - 2.25 mg/kg, and Cohort 08 - 3.0 mg/kg).



1.3.2.2. Efficacy and safety findings

The efficacy of BCD-085 in patients has not yet been investigated. Today, information is available on the efficacy of the closest analogs of BCD-085 that have the similar mechanism of action (ixekizumab, secukinumab, and brodalumab). The first 2 products contain fully human monoclonal antibodies selective for interleukin-17, and the last one contains antibodies that target the IL-17 receptor.

Phase II clinical study of ixekizumab includes 142 patients with moderate to severe psoriasis. The patients are randomized to 5 arms: 150 mg, 75 mg, 25 mg, and 10 mg of ixekizumab, and placebo. BCD-085/placebo was administered at weeks 0, 2, 4, 8, 12 and 16. The primary endpoint set as the proportion of patients who achieved a PASI75 at Week 12 of therapy was 82.1%, 82.8%, 76.7%, 29.0%, and 7.7%, respectively. The differences with the placebo arm were significant for all doses except for the 10 mg dose. In the 25 mg arm, no significant differences with the placebo arm were observed in the proportion of PASI 100 responders. The differences between the arms given 75 mg and 150 mg ixekizumab were not significant. The drug demonstrated a favorable safety profile at all doses. Adverse events included nasopharyngitis, upper respiratory tract infections, administration site reactions, and headache. The frequency of these adverse events did not exceed that in the placebo arm [15].

Results from two phase III clinical studies, UNCOVER-2 and UNCOVER-3, are expected to gain approval for ixekizumab [16]. These studies involved patients with moderate to severe plaque psoriasis ((BSA ≥ 10%, sPGA≥ 3, and PASI ≥ 12). Patients (n = 2570) were randomly assigned 1:2:2:2 to receive placebo, etanercept (50 mg twice a week), ixekizumab 80 mg every 2 weeks after the starting dose of 160 mg [IX2W arm] or ixekizumab 80 mg every 4 weeks after

[14]Genovese M.C. et al. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis. A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. // Arthritis and rheumatism. Vol.62, No.4, April 2010, pp.929-939.

the starting dose of 160 mg [IX4W arm]. The UNCOVER-2 study involved 1224 patients and UNCOVER-3 study involved 1346 patients.

At week 12, both primary endpoints (PASI 75 response and sPGA scores of 0/1 at Week 12.) were met in both studies. In the UNCOVER-2 and UNCOVER-3 trials, the PASI75 was achieved in 89.7% and 87.3% of patients, respectively (IX2W arm), in 77.5% and 84.2% of patients (IX4W arm), 2.4% and 7.3% of patients (placebo arm), and 41.6% and 53.4% of patients (etanercept arm). The sPGA response was achieved in 83.2% and 80.5% of patients, respectively (IX2W), 72.9% and 75.4% of patients (IX4W), 2.4% and 6.7% of patients (placebo arm), and 36.0% and 41.6% of patients (etanercept arm).

Serious adverse events were registered in 1.9% of patients in the IX2W arm, 1.9% of patients in the IX4W arm, 1.9% of patients in the placebo arm, and 1.8% of patients in the etanercept arm. No deaths occurred in this study. The most frequently observed AEs are listed in Table 5.

Table 5. Adverse reactions from the UNCOVER-2 and UNCOVER-3 trials.

Adverse reaction	Placebo, n=360	Etanercept, n=739	IX4W n=729	IX2W n=734
Any treatment-emergent AE	44.2%	53.9%	57.5%	57.4%
SAEs	1.9%	1.8%	1.9%	1.9%
Any infection	20.3%	21.2%	25.8%	25.3%
Nasopharyngitis	7.8%	7.4%	3.8%	8.3%
Upper respiratory tract infection	3.3%	4.6%	3.3%	3.7%
Injection-site reaction	1.1%	10.8%	8.5%	10.4%
Injection-site erythema	0.6%	3.9%	1.9%	3.3%
Injection-site pain	1.4%	1.2%	1.2%	2.9%
Pruritus	1.4%	1.1%	2.2%	1.9%
Headache	2.2%	4.2%	4.7%	4.5%
Arthralgia	2.2%	2.3%	2.5%	2.7%

Brodalumab is an antibody targeting the receptor that binds to interleukin 17A, interleukin 17F, and the heterodimeric IL-17A/F cytokine. In phase II study [17], brodalumab was given at a dose of 280 mg once a month or at a dose of 70, 140, or 210 mg at weeks 0, 1, 2, 4, 6, 8, and 10. The 75% PASI improvement at Week 12 was observed in 67%, 33%, 77%, and 82% of patients

given brodalumab, respectively. In the placebo arm, no PASI75 response was observed at all. The frequency of PASI75 response in all brodalumab arms differed significantly from that in the placebo arm. Adverse events were rare. The rate of AEs was slightly higher in the high-dose arms. Two SAEs were registered in the study (grade 3 neutropenia).

The main pivotal phase III studies with brodalumab are the AMAGINE-2 and AMAGINE-3 [18]. Patients with moderate to severe psoriasis were randomly assigned to 4 arms. Patients in Arm 1 were given 210 mg of brodalumab every 2 weeks; patients in Arm 2 - 140 mg of brodalumab every 2 weeks; patients in Arm 3 were given ustekinumab (45 mg for patients under 100 kg and 90 mg for patients ≥ 100 kg); and patients in Arm 4 were given placebo. At Week 12, patients given brodalumab were re-randomized to different drug doses: 210 mg every 2 weeks, 140 mg every 2 weeks, 140 mg every 4 weeks, and 140 mg every 8 weeks. Patients given ustekinumab continued receiving the treatment every 12 weeks, and patients from the placebo arm were given brodalumab 210 mg every 2 weeks. The endpoints were set as the proportion of patients who achieved a PASI75 at Week 12 and the proportion of patients who had the sPGA score decreased from baseline to 0/1. Two studies randomized 1831 patients; 1776 patients completed 12 weeks of treatment, and 1691 patients completed 52 weeks of treatment.

Study results are presented in Table 6. Brodalumab 210 mg given every 2 weeks was superior to ustekinumab with respect to the proportion of PASI75 responders and sPGA responders.

Table 6. Results from the AMAGINE-2 and AMAGINE-3 trials at Week 12 of treatment.

Outcome	Placebo, n=624	Ustekinumab, n=613	Brodalumab, 140 mg every 2 weeks, n=1239	Brodalumab, 210 mg every 2 weeks, n=1236
PASI75 response	7.1%	69.7%	67.9%	85.7%
sPGA response	4.0%	59.1%	59.0%	79.1%

Most of the patients retained the PASI75 and sPGA response at Week 52. The proportion of patients with an sPGA score of 0 or 1 at Week 52 was significantly higher among those who had received 210 mg or 140 mg of brodalumab every 2 weeks than among those who had received the other brodalumab maintenance regimens.

The main adverse reactions registered in the AMAGINE-2 and AMAGINE-3 trials during the induction phase (first 12 weeks) are listed in Table 7.

Table 7. Adverse reactions registered in the AMAGINE-2 and AMAGINE-3 trials during the induction phase (first 12 weeks).

Adverse reaction	Placebo, n=624	Ustekinumab, n=613	Brodalumab, 140 mg every 2 weeks, n=1239	Brodalumab, 210 mg every 2 weeks, n=1236
Any AEs	51.0%	56.3%	56.3%	57.3%
SAEs	1.8%	1.0%	1.9%	1.2%
Death	0.0%	0.0%	0.0%	0.1%
Nasopharyngitis	5.8%	5.5%	6.6%	6.2%
Upper respiratory tract infection	6.4%	5.9%	4.0%	5.1%
Headache	3.7%	3.8%	5.4%	4.2%
Arthralgia	5.1%	2.4%	4.7%	5.2%
Injection site reaction	1.4%	2.0%	1.6%	1.5%

In November 2014, Amgen and AstraZeneca announce positive results from a phase III trial, according to which brodalumab was shown superior to ustekinumab and placebo.

Secukinumab is a monoclonal antibody targeting interleukin-17. In January 2015, the U.S. FDA approved secukinumab for the treatment of moderate to severe plaque psoriasis.

A phase II study [19] involved 125 patients with moderate to severe plaque psoriasis. These patients were given placebo or a single injection of 25 mg secukinumab, or 25 mg, 75 mg or 150 mg of secukinumab every month. The PASI75 at week 12 was set as the primary endpoint, which was achieved in 9% of patients given placebo, 4% of patients given a single 25 mg dose of secukinumab, and in 18%, 57.1%, and 81.5% of patients given 25 mg, 75 mg, and 150 mg of secukinumab once a month. The drug showed a favorable safety profile. The most common AEs were a progression of the main disease, nasopharyngitis, and upper respiratory tract infections.

Another phase II study [20] used multiple dosing regimens in 404 patients. As an induction therapy, the patients were given a single dose of secukinumab (Week 0) or secukinumab weekly injections (weeks 0, 1, 2, 4, and 8). As a maintenance treatment (weeks 12-36), the patients were

given either injections at weeks 12 and 24 ("fixed interval" regimen) or injections on an on demand basis ("start of relapse" regimen). During the induction phase, the proportion of PASI75 responders was higher in the arms given secukinumab every month or more frequently as compared to the placebo arm (54.5% and 42.0% *vs.* 1.5%). In the maintenance phase, the number of patients was assessed who achieved a PASI75 at least once from Week 20 to Week 28. The regular dosing regimen was shown beneficial. (84.6% *vs.* 67.2%). The most frequently observed AEs were disease progression, nasopharyngitis, and headache.

Secukinumab was approved on the basis of the findings from two pivotal phase III studies: ERASURE and FIXTURE [21]. These studies involved patients with moderate to severe plaque psoriasis, PASI score of 12 or higher and IGA mod of 3 or 4, and a total BSA of minimally 10%.

Patients in the ERASURE study were randomly assigned to 3 arms: secukinumab 300 mg, secukinumab 150 mg, or placebo. Patients in the FIXTURE study were randomized to 4 arms: secukinumab 300 mg, secukinumab 150 mg, etanercept, or placebo.

Patients from secukinumab arms were given the drug at weeks 0, 1, 2, 3, and 4, and then every 4 weeks for 48 weeks. Patients from the etanercept arm were given 2 injections twice a week until Week 12 and then once weekly up to Week 51.

Study results are presented in Tables 8 and 9.

Table 8. Results from the ERASURE study at Week 12 of treatment.

Outcome	Placebo, n=246	Secukinumab 300 mg n=245	Secukinumab 150 mg n=243
PASI75 response	4.5%	81.6%	71.6%
sPGA response	2.4%	65.3%	51.2%

Table 9. Results from the FIXTURE study at Week 12 of treatment.

Outcome	Placebo, n=246	Secukinumab 300 mg n=245	Secukinumab 150 mg n=243	Etanercept, n=323
PASI75 response	4.5%	77.1%	67.0%	44.0%
sPGA response	2.8%	62.5%	51.1%	27.2%

In the ERASURE study, the number of patients who had at least one AE was higher in secukinumab arms than in the placebo arm (55.1% in the 300 mg arm, 60.4% in the 150 mg arm, and 47% in the placebo arm). Infections and infestations were significantly more frequent with secukinumab than with placebo (29.4%, 26.9%, and 16.2%, respectively). The most common AEs were nasopharyngitis, headache, and upper respiratory tract infections.

In the FIXTURE study, the safety parameters were similar between secukinumab and etanercept. Injection site reactions were rarer in secukinumab arms (0.7% vs. 11.1%). The incidence of adverse events is presented in Table 10.

Table 10. Adverse reactions in the FIXTURE study during the induction phase (first 12 weeks).

Adverse reaction	Placebo, n=246	Secukinumab 300 mg n=245	Secukinumab 150 mg n=243	Etanercept, n=323
Any AEs	49.8%	55.5%	58.4%	57.6%
SAEs	1.8%	1.2%	2.1%	0.9%
Nasopharyngitis	8.0%	10.7%	13.8%	11.1%
Upper respiratory tract infection	6.4%	5.9%	4.0%	5.1%
Headache	7.0%	9.2%	4.9%	7.1%
Diarrhea	1.8%	5.2%	3.7%	3.4%
Pruritus	3.4%	2.5%	3.7%	2.5%
Arthralgia	3.1%	1.5%	4.3%	3.7%
Upper respiratory tract infection	0.9%	2.1%	3.1%	2.2%
Back pain	1.8%	2.5%	2.4%	2.8%
Cough	1.2%	3.4%	1.5%	1.2%
Arterial hypertension	1.2%	1.5%	3.1%	1.5%
Nausea	2.1%	2.5%	1.8%	1.2%
Pain in the mouth or throat	2.1%	2.8%	1.5%	1.2%

Thus, all three products blocking the signaling of interleukin-17 demonstrated high efficacy and favorable safety in clinical trials.

1.3.3. Conclusions and study rationale

Psoriasis is a common skin disease. In Russia, about 100 000 new cases of psoriasis are registered every year. Despite a significant progress in the development of treatment options, severe atypical forms resistant to therapy have become more common in the last decade. Biologics containing monoclonal antibodies are considered the most effective agents to treat these forms of psoriasis.

The current knowledge about the mechanisms of psoriasis indicates the crucial role of interleukin-17 in the skin damage. Considering this information, a number of monoclonal antibody drugs have been developed selectively targeting either interleukin-17 or its receptor. The high efficacy and favorable safety profiles of the new biologics were confirmed in a number of clinical studies.

JSC BIOCAD has developed an original monoclonal anti-IL-17 antibody (BCD-085), which [redacted]

The physicochemical studies of BCD-085 have characterized its primary, secondary, and tertiary structure, glycosylation pattern, purity and homogeneity, and *in vitro* binding to the antigen [redacted] the suppression of inflammation. The drug was well tolerated by experimental animals and was considered low-toxic. Experiments were also conducted to characterize the pharmacokinetics of the drug.

Results obtained in a comprehensive non-clinical program allowed conducting phase I clinical study in healthy volunteers. This study confirmed the previously discovered characteristics: low toxicity and good tolerability of the drug. Pharmacokinetics of BCD-085 demonstrated in this study was typical for monoclonal antibodies. The drug has a long elimination half-life.

Thus, BCD-085 can be recommended for further clinical development in the target population of patients. With the current knowledge from clinical studies of other drugs having similar mechanisms of action, psoriasis is believed to be highly sensitive to the IL-17 blockade. Investigating it in the population with moderate to severe plaque psoriasis will allow evaluating the therapeutic potential and characterize the safety of an innovative drug BCD-085.

1.4. Brief description of known and potential risks and benefit for study subjects (benefit/risk balance)

1.4.1. Benefit assessment

BCD-085 is an innovative drug the toxicity, safety, and pharmacokinetics of which was investigated in animals and in phase I clinical study in healthy volunteers. On the basis of the known biological effects of interleukin-17 and its role in the pathogenesis of autoimmune diseases, it is believed that the use of this drug in psoriasis patients will significantly reduce the inflammation and the severity of cutaneous and joint (if available) components, prevent stigmatization and early disability and improve the quality of life. The initiated clinical trial aims at defining the effective dose in a limited population, which means that some of the study subjects may not get any personal benefit from the study, except for a detailed medical examination. However, study results will be of high scientific value and, potentially, will help to introduce in clinical practice a highly effective medicine for the treatment of severe autoimmune diseases.

1.4.2. Risk assessment

BCD-085 is a new drug, so its effects in humans are not enough investigated. PD effects of blocking human IL-17 [redacted] that BCD-085 may increase the risks of infections, including severe ones, and reactivation of latent opportunistic infections. However, BCD-085 in this study will be given to patients only after they undergo a complete screening examination (including that for chronic infections). Thus, it is expected that the risk of infectious complications for the patients involved in the study will be minimal. A risk of allergic reactions cannot be ruled out in subjects with hypersensitivity to ingredients of BCD-085. The method of administration (SC) and protein nature of BCD-085 suggest that there is a risk of injection site reactions.

BCD-085 is a highly organized protein molecule with targeted immunotropic effects. Thus, it is necessary to identify potential risks of acute immune reactions after its first administration in humans.

[redacted]

[redacted]

[redacted] Non-clinical studies reliably showed that BCD-085 does not have any cytotoxicity, does not lead to acute immune reactions at the injection site or adjacent areas, and does not have any cross-reactivity to human tissues. These results are also substantiated by the available data gained during the use of drugs with a similar mechanism of action (ixekizumab, secukinumab, brodalumab). BCD-085 does not have any pathogenetic mechanisms that can lead to acute immune reactions (which are not related to immediate-type hypersensitivity). Therefore, these reactions are unlikely to occur [redacted]

A completed phase I clinical study in healthy volunteers demonstrated that SC injections of BCD-085 at a wide range of doses (0.05 mg/kg to 3.0 mg/kg) rarely is associated with any adverse events, among which there were cases of elevated liver transaminases and one event of neutropenia. All AEs were mild (severity grade 1, CTCAE), short-term, and successfully resolved in all patients. It is assumed that the risk of such conditions or their more severe forms among the participants of this clinical study is minimal.

1.4.3. Conclusions

Findings from the physicochemical investigation, non-clinical development, and clinical studies of PK, safety, and tolerability in healthy volunteers provide the evidence of the favorable safety profile of BCD-085 and its potential efficacy in chronic inflammation. Thus, it is expected that the use of BCD-085 in the further clinical program, including in patients with psoriasis, will have a positive outcome with the low risk of adverse reactions. Thus, the overall risk/benefit balance with BCD-085 is considered favorable for the patients.

1.5. Description and justification of the route of administration, dosing regimen, and treatment course

1.5.1 Description and justification of the study design

This clinical trial was designed as a multicenter, double-blind, randomized study of the efficacy and safety to be run in 4 parallel arms, patients in 3 of which will receive different doses of BCD-085 (40 mg, 80 mg, and 120 mg), and patients in one arm will receive placebo.

Since the planned population size is 120 patients with moderate to severe plaque-type psoriasis, it is unlikely that all of them can be recruited at one study site. To ensure the optimal timing, patients will be recruited at several sites.

In this study, effects of BCD-085 will be compared with the effects of placebo to make adequate and objective conclusions on the efficacy and safety of the test product. The use of placebo is a standard approach in the clinical development of systemic medications for the treatment of psoriasis, which can be illustrated by clinical studies of ixekizumab, brodalumab, and secukinumab [15-21]. The necessity of using a placebo in the development of systemic medications is also mentioned in the EMA's guidelines on clinical investigation of medicinal products for the treatment of psoriasis [CHMP/EWP/2454/02 corr, 2004].

The double-blind design is used to reduce the bias during the physician's and patient's assessment of treatment results, minimize systemic errors, and, therefore, to improve the validity of study results.

The test drug and placebo will be given in parallel to patients in different arms. This is important to obtain objective results and eliminate the possibility of external factors to affect the treatment efficacy and safety. It is known, for example, that psoriasis patients commonly have seasonal exacerbations, and by using the parallel-group design, we eliminate the effect of the season on the study results.

Randomization ensures that any factors that can affect treatment results are uniformly distributed by study groups, thus allowing investigators to attribute differences in responses directly to the investigational product used.

One of the objectives of the phase II study is to find the effective dose and dosing regimen for the drug being investigated. At early development, the treatment duration should be enough to establish the efficacy and safety of the drug but should not be too long because not all doses used will produce the best possible benefit. The EMA guidelines [CHMP/EWP/2454/02 corr, 2004]

state that the primary efficacy data in the population of psoriasis patients can be obtained after the drug was used for 8 to 12 weeks [CHMP/EWP/2454/02 corr, 2004].

The primary endpoint of this study is the proportion of patients with a PASI 75 response at Week 12. This is a sensitive indicator for patients with moderate to severe plaque psoriasis. It should be noted that a treatment duration of 12 weeks with an assessment of the proportion of PASI75 responders is widely used in clinical development to evaluate the efficacy of psoriasis drugs and is recommended in the EMA's guidelines on clinical investigation of medicinal products indicated for the treatment of psoriasis [EMEA/CHMP/EWP/2454/02 corr, 2004]. This approach had been used in phase II clinical studies of ixekizumab, brodalumab, and secukinumab [15, 17, 19, 20].

The use of the PASI alone may not be enough for the throughout efficacy assessment, so the clinical course of psoriasis in the study will be comprehensively assessed by using the changes in the body surface area (BSA) affected by psoriasis, static Physician's Global Assessment (sPGA), nail psoriasis severity index (NAPSI), absolute PASI values, and other indicators. This is consistent with the recommendations stated in the EMA's Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis [EMEA/CHMP/EWP/2454/02corr, 2004].

The recent findings suggest that interleukin-17 pays a key role in the development of psoriasis. Clinical studies of drugs blocking the IL-17 signaling (ixekizumab, brodalumab, and secukinumab) demonstrate high efficacy of this approach in the treatment of patients with moderate to severe plaque-type psoriasis with the PASI75 response seen in 70% to 80% of patients as early as at Week 12 of treatment. Thus, moderate to severe plaque-type psoriasis is considered a sensitive enough model for clinical investigation of BCD-085.

1.5.2. Description and justification of the route of administration, dosing regimen, and treatment course

Patients will be given BCD-085 at a dose of 40/80/120 mg or placebo as SC injections on Day 1/Week 0, Day 1/Week 1, Day 1/Week 2, Day 1/Week 4, Day 1/Week 6, Day 1/Week 8, and Day 1/Week 10. The patients will be followed up until Week 14 after the first dose.

BCD-085 is a potential therapeutic candidate for the long-term management of psoriasis. To make the drug more convenient for the patients, it is planned to be used as SC injections. This route of administration has several advantages: patients can give injections to themselves, or injections can be made in the outpatient settings. Thus, it is reasonable to study the efficacy, safety,

pharmacokinetics, and immunogenicity of BCD-085 in patients with the same route of administration that is planned to be implemented in routine clinical practice.

The doses of BCD-085 and the dosing frequency used in this study were chosen based on the available information on approved anti-IL-17 monoclonal antibodies and those under development. The most investigated drugs in this category are ixekizumab (Eli Lilly, USA), which is now in phase III trials, and secukinumab (Cosentyx®, Novartis, Switzerland), which is the only anti-IL-17 monoclonal antibody approved for human use.

[redacted]

In phase I study of BCD-085, all tested doses (including those exceeding the expected therapeutic dose) demonstrated the favorable safety profile. Therefore, no increased risk is expected for patients who will be given BCD-085 at doses different from the planned effective dose.

The main PK parameters of ere characterized in a phase I trial. This trial involved several cohorts of healthy volunteers who were given SC injections of BCD-085 at doses calculated per 1 kg of the body weight and individual for each cohort (details are presented in section 1.3.2). Clinical trials

It has been shown that doses closest to those planned to be used in phase II trial were given to patients from cohorts 4-6 (with an account for patients body weight). Thus, it is considered that BCD-085 at doses of 40 mg, 80 mg, and 120 mg will have pharmacokinetics similar to that seen

[15] Cosentyx® Assessment report, EMA/CHMP/389874/2014, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Public_assessment_report/human/003729/WC500183131.pdf

[16] Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators.Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomized trials.Lancet. 2015 Aug 8;386(9993):541-51.

in cohorts 4-6 with the half-life of 16 to 18 days. Based on this, BCD-085 injections should be given with an interval of about 2 weeks.

At baseline, patients have an acute inflammation that has to be resolved as soon as possible. This requires using induction (higher) doses or an induction phase (more frequent injections). Clinical trials of drugs inhibiting the signaling of interleukin-17 utilize both the first [16] and the second [17, 18, 20, 21] approaches. In this study, patients will receive BCD-085 once weekly during the induction phase. Then they will be transferred to the maintenance phase and receive the drug once every 2 weeks.

Thus, the doses (40 mg, 80 mg, and 120 mg), regimen, and route of administration to be used in this study were chosen on the basis of the findings from non-clinical and phase I clinical studies of BCD-085 and available information on other anti-IL-17 monoclonal antibodies, taking convenience to patients into account.

1.5.3. Justification of placebo use

About every 4th patient in this study will receive placebo. This is necessary to draw unbiased conclusions on the efficacy and safety of the study drug and is a standard approach for investigating systemic medications for psoriasis. The necessity of using a placebo in the development of systemic medications is also mentioned in the EMA's guidelines on clinical investigation of medicinal products for the treatment of psoriasis [CHMP/EWP/2454/02 corr, 2004].

Patients involved in this study will net be exposed to excessive risk because of getting a placebo. All patients are allowed to continue systemic non-biologic medications and, in some cases, glucocorticoids. Topical glucocorticoids will be permitted to be used on the face, armpits, and genitals. If the disease worsens and requires additional therapy, patients can always discontinue the study and receive all the medications he/she needs. It should also be noted that the therapeutic effect of BCD-085 in psoriasis patients has not yet been investigated, so we cannot clearly state the benefit of being in the active-treatment arm.

This being said, the use of placebo in one of the arms does not pose any threat to the patients' safety and is in full compliance with the international guidelines and practice of studies of medicinal products for the treatment of psoriasis.

1.6. Clinical study compliance with the regulatory requirements

This clinical study will be conducted in accordance with the Protocol. The clinical study was developed in compliance with the GCP principles, current law and regulatory requirements of the participating countries.

1.7. Description of study population

Males and females aged from 18 to 65 years, who had with stable moderate to severe plaque psoriasis and who did not respond to or were candidates for systemic therapy including TNF-α inhibitors or UV therapy.

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2. STUDY PURPOSE AND OBJECTIVES

2.1 Study aims

Study purpose: To find an effective and safe dose of BCD-085 for multiple injections in patients with moderate to severe plaque-type psoriasis.

2.2 Study objectives

1. To determine the number of patients in each study arm who achieved a PASI 75 at Week 12 of treatment
2. To determine the number of patients in each study arm who achieved a PASI 75 at weeks 4 and 8 of treatment
3. To determine the number of patients in each study arm who achieve a PASI 50/90 at weeks 4, 8, and 12 of treatment
4. To evaluate the PASI improvement from baseline in each study arm at weeks 4, 8, and 12.
5. To evaluate the improvement from baseline in the body surface area (BSA) affected by psoriasis in each study arm at weeks 4, 8, and 12
6. To evaluate the improvement from baseline in the nail psoriasis severity index (NAPSI) in each study arm at weeks 4, 8, and 12
7. To determine the mean improvement from baseline in the intensity of pruritus measured by VAS (0-100 mm) in each study arm at weeks 1, 4, 8, and 12
8. To evaluate the proportion of patients in each study arm who achieve an sPGA score 0 or 1 at weeks 4, 8, and 12 relative to baseline
9. To investigate patients' quality of life in each study arm at weeks 4, 8, and 12 according to SF-36 and DLQI.
10. To evaluate the proportion of patients in each study arm who develop adverse events with repeated administration of 40 mg, 80 mg, and 120 mg BCD-085 as compared to placebo

[redacted]

[redacted]

3.0 HYPOTHESIS

This clinical study is based on the hypothesis that the clinical efficacy of BCD-085 defined based on the proportion of patients with moderate to severe plaque psoriasis who achieved a PASI75 at Week 12 of treatment is higher than the same effect seen with placebo.

4. STUDY DESIGN

4.1. Primary and secondary endpoints

4.1.1 Primary endpoint

- The proportion of patients in each study arm who achieved a PASI 75 at Week 12 of treatment

4.1.2 Secondary endpoints

Efficacy endpoints:

- The proportion of patients in each study arm who achieved a PASI 75 at weeks 4 and 8 of treatment
- The proportion of patients in each study arm who achieved a PASI 50/90 at weeks 4, 8, and 12 of treatment
- The relative PASI improvement from baseline in each study arm at weeks 4, 8, and 12
- The relative BSA improvement from baseline in each study arm at weeks 4, 8, and 12
- The relative NAPSI improvement from baseline in each study arm at weeks 4, 8, and 12
- The mean change from baseline in the intensity of pruritus measured by VAS (0-100 mm) in each study arm at weeks 1, 4, 8, and 12
- The proportion of patients in each study arm who achieved an sPGA score 0 or 1 at weeks 4, 8, and 12 relative to baseline

[17] If neutralizing antibodies are detected in the serum samples collected for PK study.

- The mean change from baseline in the QoL score in each study arm (assessed using the DLQI and SF-36 scales) at weeks 4, 8, and 12.

Safety endpoints:

- The proportion of patients who developed SAEs
- The proportion of patients who developed AEs
- The proportion of patients who developed administration site reactions
- The proportion of patients who developed grade 3/4 AEs/SAEs
- The proportion of patients who discontinued the study due to AEs/SAEs.

[redacted]

4.2. Description of the study type/design, study flow-chart, study procedures and periods

Study design

This international multicenter study uses a double-blind comparative design. The purpose of the study is to determine a therapeutically effective dose of BCD-085 to be repeatedly administered in patients with moderate to severe plaque-type psoriasis, as compared with placebo.

The study is planned to include 120 adults who had moderate to severe plaque psoriasis stable for at least 6 months before inclusion in the study (i.e. there were no changes in morphological appearance, no severe aggravation or worsening of the disease occurred during this time, as judged by the investigator), 10% or greater body-surface area involvement, a psoriasis area and severity index (PASI) of 12 or more, and a sPGA score of 3 or more.

Before being included in the study, patients must read and sign the informed consent form and undergo a screening examination (not longer than 4 calendar weeks) to confirm that they are eligible for the study. The Protocol does not stipulate any additional requirements for the diet or physical activity during the screening or study period.

Stratification and randomization

When all screening procedures are completed and the investigator approves patient's inclusion in the study, patients are stratified by body weight (≤ 80 kg / ≥81 kg), prior use of monoclonal antibodies for psoriasis (MAb-treated / MAb-naive), current use of systemic non-biologics (yes/no), PASI score (< 20 / ≥ 20), signs of psoriatic arthritis (absent / present). After stratification, the patients are randomized 1:1:1:1 to one of four study arms:

- **Arm 1:** patients will receive subcutaneous injections of 40 mg BCD-085 (1.0 mL) once a week for the first 3 weeks (induction period) and then once every 2 weeks (maintenance period). For blinding purposes, these patients will be given two SC injections of placebo (1.0 mL each) together with each injection of BCD-085. Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period).
- **Arm 2:** patients will receive 80 mg BCD-085 (two SC injections 1.0 mL each) once a week for the first 3 weeks (induction period) and then once every 2 weeks (maintenance period). For blinding purposes, these patients will be given one SC injection of placebo (1.0 mL) together with the injections of BCD-085. Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period).
- **Arm 3:** patients will receive 120 mg BCD-085 (three SC injections 1.0 mL each) once a week for the first 3 weeks (induction period) and then once every 3 weeks (maintenance

period). Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period).

- **Arm 4:** patients will receive placebo as three 1.0 mL SC injections on Day 1/Week 0, Day 1/Week 1, Day 1/Week 2, Day 1/Week 4, Day 1/Week 6, Day 1/Week 8, and Day 1/Week 10.

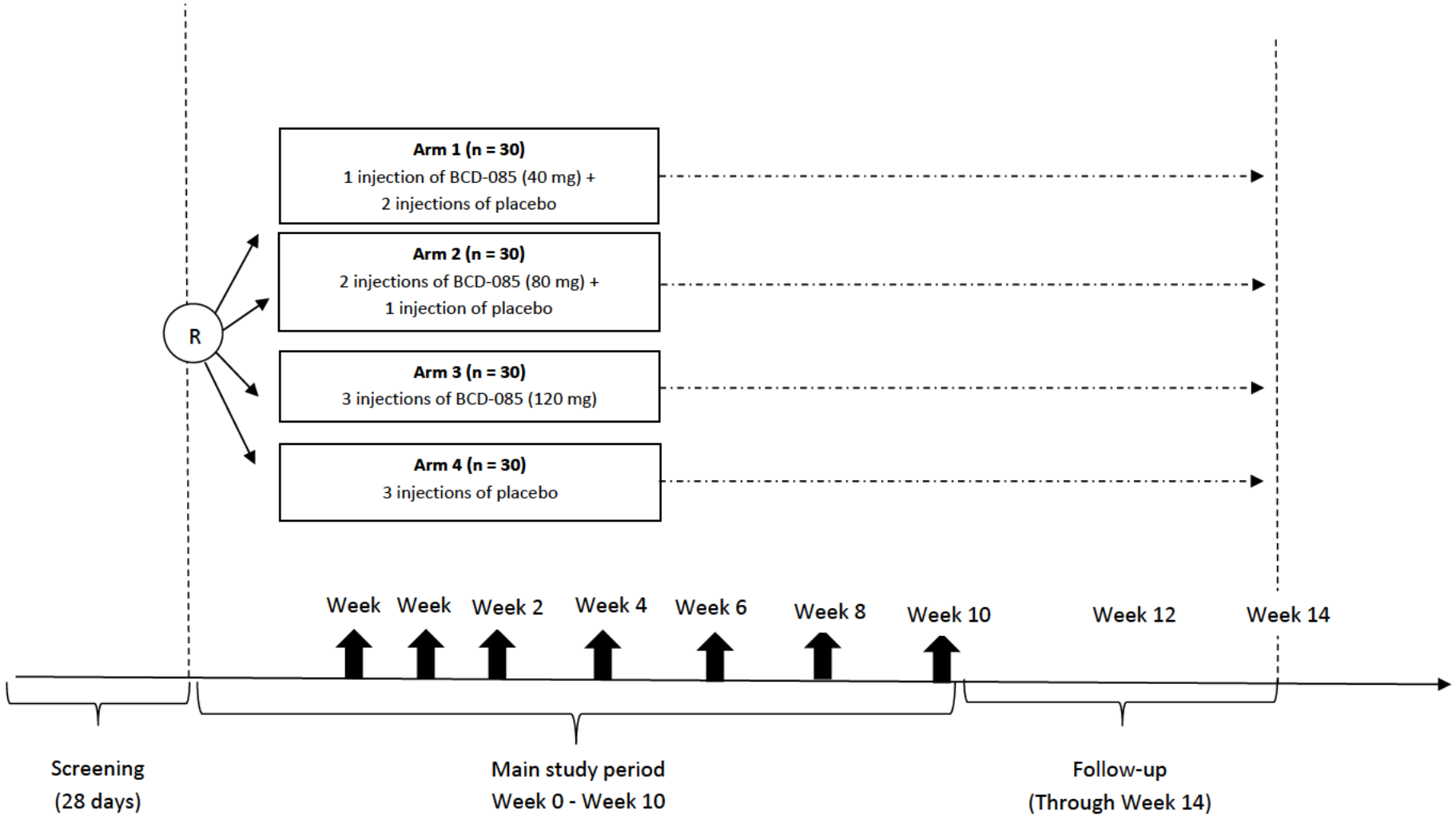
Because patients included in the PK analysis will be requested to provide multiple blood specimens during the first 24 h after the first injection, these patients may stay at the study site at the discretion of the investigator.

Study periods

- Screening (not more than 4 calendar weeks)
- Therapy period: induction period and maintenance period: from Week 0 to Week 10
- Follow-up: 4 calendar weeks (through Week 14)

Nine visits to study sites are planned during 14 weeks of the active study period. During these visits, blood samples will be drawn for the efficacy, safety, [redacted]

Figure 5. Study flow-chart.



Treatment by study arms

In this study, BCD-085 will be administered to patients in three of four study arms. Patients will receive 40 mg, 80 mg, or 120 mg BCD-085 as SC injections once weekly for the first three weeks (induction regimen) and then once every two weeks (maintenance regimen). Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period).

For blinding purposes, patients from 40 mg and 80 mg arms will receive two or one SC injection of placebo (1 mL each), respectively.

Patients in the control arm will receive 3 SC injections of placebo (each injection is 1.0 mL). Placebo to be used has the similar composition for all three arms and contains the same excipients that the BCD-085 dosage form.

Regardless of the arm to which the patient is assigned, injections will be performed by an authorized site medical nurse directly in the study site. Injections can be given to the abdomen, hips, or upper arms. Injections should be given at least 5 cm apart.

During the entire study period, patients are not allowed to use phototherapy (UV-B), photochemotherapy (PUVA), biologics other than BCD-085, and live or attenuated vaccines.

The patients are allowed to use systemic non-biologic therapies (methotrexate, sulfasalazine, chlorambucil, leflunomide, cyclosporine A, azathioprine, aromatic retinoids (acetretin), and glucocorticoids (> 10 mg of prednisolone equivalent per day) if their dose was stable for 4 weeks before signing the informed consent and through the entire screening period). Patients are not allowed to change their systemic non-biologic treatment during the study, increase the dose, or add any new medications of this category. Patients are allowed to discontinue systemic non-biologic therapies only if he/she has any life- or health-threatening adverse effects due to this treatment. Any modifications of the dosing regimen or dose reduction for systemic non-biologic therapy can be made only after reconciliation with the Sponsor.

The patients may use topical glucocorticoids on the face, underarm, and genitals. The patients may use topical moisturizing products, emollients, oils or salicylic acid-based products if necessary. The patients should discontinue all local skin products (medications or cosmetics) 24 hours before the planned PASI assessment.

Management of patients after the end of the study

Management and follow-up of patients who completed/discontinued the study due to any reason are to be defined by the attending physician.

Study procedures

To establish whether patients meet the inclusion/exclusion criteria and to assess the treatment efficacy (for enrolled subjects), patients will undergo, within the timeframes specified by the Protocol, a comprehensive medical exam including:

- Taking baseline clinical characteristics and medical history
- Physical examination
- Measuring blood pressure and wrist pulse
- Electrocardiography
- Chest X-ray / fluorography (front view)
- Blood hematology
- Blood biochemistry
- Pregnancy test[18]
- Assessment of the patient's infection status (Diaskintest® or blood testing for interferon gamma (QuantiFERON test)); if these tests are impossible to perform, the Mantoux test can be done and the patient can be examined by the TB specialist (required if the Diaskintest® or QuantiFERON test results are uncertain or if the Mantoux results are uncertain or positive), anti-HIV antibodies [HIVAg/Ab Combo], HBs-antigen, anti-HBcor antibodies [IgG + IgM/ IgG/ IgM], and anti-HCV antibodies [IgG + IgM], qualitative PCR for HCV RNA / HBV DNA (only if the patient was positive for respective antibodies), consultation with an infectious disease specialist (required only if the patient is positive for anti-HBcor antibodies or anti-HCV antibodies), microprecioitation reaction, and a direct hemagglutination assay (T. pallidum)
- Calculation of the body surface area affected by psoriasis (BSA)
- Assessment of the area and severity of psoriasis with the PASI score
- Assessment of psoriasis severity with sPGA[19]
- The severity of pruritus assessed with the visual analog scale (0-100 mm)
- Assessment of psoriasis involvement of nails (NAPSI)
- DLQI and SF-36 questionnaires.

To measure the efficacy of treatment in the timeframes specified by the Protocol, the changes over time in the PASI, NAPSI, and sPGA scores, VAS scores for pruritus intensity, and the quality of

[18] Pregnancy test is required only for women of childbearing potential and does not apply to post-menopausal women.
[19] Static Physicians Global Assessment.

life (DLQI and SF-36 scores) will be evaluated. [redacted]

For safety evaluation, the following will be closely monitored: all general disorders (including fever and flu-like symptoms), abnormal physical signs (BP, wrist pulse), infections, abnormalities in certain laboratory values (CBC results: hemoglobin, RBC, platelets, WBC including changes in the WBC differential, ESR; blood biochemistry: glucose, total bilirubin, indirect bilirubin, ALT, AST, GGT, LDH, total protein, creatinine, urinalysis; coagulation profile: prothrombin ratio, APTT), cardiac disorders (ECG), lung abnormalities (chest X-ray / fluorography).

[redacted]

4.3. Measures to minimize/eliminate bias

4.3.1. Distribution of patients by study sites

Patients' recruitment at study centers will be performed on a competitive basis. After the inclusion of the 120th patient, recruitment to the study will be stopped. Recruitment can be re-opened if the Sponsor's audit reveals patients who do not meet the eligibility criteria or patients who majorly violate the Protocol (with no explanation timely provided to the Sponsor).

4.3.2. Procedure of assigning study IDs

Patients will be randomized, stratified, and assigned study numbers according to internal guidelines of JSC BIOCAD.

Each study site will be assigned a 2-digit ID number. For example, the first site will be numbered 01, the second – 02, the third – 03, etc.

After signing an informed consent form, each patient will receive a 5-digit screening number consisting of a 2-digit center number and a 3-digit patient's number (continuing numbering in sequence, as patients are enrolled in this center). This should be recorded in source documents and a patients' screening log. For example, in the study center 02, the first patient who

has signed an informed consent form will receive the screening number 02-001.

When all screening procedures are completed, and the Investigator decides that the patient conforms to all inclusion criteria and none of the non-inclusion criteria, the Investigator fulfills a screening form and sends it to the clinical study project manager of JSC BIOCAD by e-mail or fax: [redacted] If JSC BIOCAD confirms the inclusion of this patient, a BIOCAD's representative stratifies and randomizes the patient, assigns him/her a Patient ID, and e-mails a Randomization Form (with the Patient ID and the drug lot number to be used in this patient) to the investigator. The investigator must record the subject's number and lot No in the source documents and the CRF.

The subject's number consists of 5 digits: 2 digits for the study site and 3 digits for the subject's number in the study. For example, subject's number is "01-112", where

"01" is the site number,

and "112" is the order number as the subject was included in the study.

Investigators can also use the centralized electronic randomization system. In this case, the investigator e-mails the screening form, receives a confirmation from BIOCAD regarding the inclusion of the patient and performs stratification and randomization via the electronic randomization system. The Patient ID and the individual drug lot number are generated automatically.

4.3.3. Stratification procedure

Before randomization, in order to make the arms as balanced as possible, patients will be stratified.

Stratification will be performed by the following criteria:

- Body weight (< 80 kg / 81 kg and more)
- Previous use of tumor necrosis factor alpha inhibitors or other monoclonal antibodies for the treatment of psoriasis (experienced / naive)
- Current treatment with systemic non-biologic drugs (yes / no)
- PASI score (< 20 / 20 or greater)
- Psoriatic arthritis (yes/no).

Table 11. Description of the strata.

Stratum	Parameters
Stratum 1	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20

Stratum	Parameters
	• Psoriatic arthritis - No
Stratum 2	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - Yes
Stratum 3	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - No
Stratum 4	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - Yes
Stratum 5	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - No
Stratum 6	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - Yes
Stratum 7	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - No
Stratum 8	• Body weight < 80 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - Yes
Stratum 9	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - No
Stratum 10	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20

Stratum	Parameters
	• Psoriatic arthritis - Yes
Stratum 11	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - No
Stratum 12	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - Yes
Stratum 13	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - No
Stratum 14	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - Yes
Stratum 15	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - No
Stratum 16	• Body weight < 80 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - Yes
Stratum 17	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - No
Stratum 18	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - Yes
Stratum 19	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20

Stratum	Parameters
	• Psoriatic arthritis - No
Stratum 20	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - Yes
Stratum 21	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - No
Stratum 22	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - Yes
Stratum 23	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - No
Stratum 24	• Body weight of ≥ 81 kg • The patient has not received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - Yes
Stratum 25	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - No
Stratum 26	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - Yes
Stratum 27	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - No
Stratum 28	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient does not receive systemic non-biologic therapy • PASI ≥ 20

Stratum	Parameters
	• Psoriatic arthritis - Yes
Stratum 29	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - No
Stratum 30	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI < 20 • Psoriatic arthritis - Yes
Stratum 31	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - No
Stratum 32	• Body weight of ≥ 81 kg • The patient has received monoclonal antibodies before • The patient receives systemic non-biologic therapy • PASI ≥ 20 • Psoriatic arthritis - Yes

Thus, after stratification, the arms will be balanced by the said characteristics.

4.3.4. Randomization procedure

Randomization in the study will be centralized. Patients will be randomly assigned 1:1:1:1 to four arms.

Patients included in the study will be randomized within each stratum (block randomization). Thus, after stratification, the arms will be balanced by all specified characteristics.

Block randomization can be described as follows. The random sequence generator generates infinite random sequences consisting of the numbers from 1 to 24 (1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24). Each number (1 to 24) corresponds to one of 24 possible unique blocks (see Table 12). As the study design does not define in advance the exact number of patients in each of the 32 strata, the patients will be randomized within each stratum to assure the equal distribution among the arms. Therefore, each stratum will contain its own block sequence (symbols “1”, “2”, “3”, and “4” corresponding to the 1:1:1:1 distribution).

Table 12. Examples of blocks for block randomization.

Block	Principle of assigning to treatment arms
#1	1,2,3,4
#2	1,2,4,3
#3	1,3,2,4
#4	1,3,4,2
#5	1,4,2,3
#6	1,4,3,2
#7	2,1,3,4
#8	2,1,4,3
#9	2,3,1,4
#10	2,3,4,1
#11	2,4,3,1
#12	2,4,1,3
#13	3,1,2,4
#14	3,1,4,2
#15	3,2,1,4
#16	3,2,4,1
#17	3,4,1,2
#18	3,4,2,1
#19	4,1,2,3

Block	Principle of assigning to treatment arms
#20	4,1,3,2
#21	4,2,1,3
#22	4,2,3,1
#23	4,3,2,1
#24	4,3,1,2

These blocks consist of an equal number of the following symbols: “1”, “2”, “3”, and “4”, with each number corresponding to one of the study arms: “1” - Arm 1; “2” - Arm 2; “3” - Arm 3; and “4” - Arm 4.

A table containing a random block sequence will be formed. Each stratum will be assigned an infinite random sequence of blocks (an example is shown in the Table below).

Table 13. An example of assigning strata with block sequence.

Stratum	**Block sequence**
Stratum 1	#1
	#6
	#5
	#2
	…
Stratum 2	#4
	#3
	#5
	#1
	…
Stratum 3	#5
	#5

Stratum	Block sequence
	#1
	#4
	…
…	…

During randomization, the BIOCAD's Clinical Study Manager allocates the patient to an appropriate stratum, assigns him/her the first free arm number in the block and a 3-digit randomization number coding this arm (corresponds to the patients's order number in the study). After randomization, the Clinical Study Manager assigns the patient an investigational product lot number (corresponding to the treatment arm) and a Patient ID. The investigator will know only the subject's ID and investigational product lot number.

For example, the first patient in the study from site #02 is allocated to stratum #2. In this case, he/she receives the first free number of the first block (the first block in this stratum) – 1. Therefore, the patient is allocated to Arm 1 (e.g. the arm treated with BCD-085). After that, the patient is assigned a corresponding 3-digit randomization code (an order number as the patient was included in the study), for example, "001" for the first patient, "002" for the second patient, etc. The investigator will be notified about the Patient ID (consisting of the site number and the sequential subject's number in the study – "02-001") and the lot number of the investigational product that the subject is to receive.

Investigators can also to use an electronic centralized randomization system based on the same principles. In this case, the investigator mails the screening form, receives a confirmation from BIOCAD regarding the inclusion of the patient, and performs stratification and randomization via the electronic randomization system. The Patient ID and the individual drug lot number are generated automatically. All numbers will be automatically generated by the system after the investigator enters all the required information.

The investigator must record the Patient ID and lot No in the source documents and the CRF.

JSC BIOCAD should keep the lists of patients' screening and randomization numbers with their randomization groups, lot and batch numbers of the investigational products.

A representative of JSC BIOCAD will monitor the total number of enrolled patients. Patient recruitment will be stopped after inclusion of the 120th patient.

4.3.5. Blinding and subject-specific lots of investigational products

Neither investigators, not patients will be aware of whether the active treatment or placebo is used in each particular patient. The investigator (the principal investigator, a co-investigator responsible for the therapy of this patient) receives BCD-085/placebo in identical secondary packaging (cartons). The drugs differ only by their lot numbers. The lot number is individual for the subject. During therapy, the subject may receive the investigational product of several batches but they will be assigned the same lot number.

[redacted]

Individual kits for the patients in each arm will be prepared to be used at scheduled timepoints (Week 0, Week 1, Week 2, Week 4, Week 6, Week 8, and Week 10). Each kit contains 3 visually indistinguishable pre-filled syringes according to the arm to which the patient is assigned:

[redacted]

Each kit includes extra packs of the patient-specific lots to be used if any of the pre-filled syringes specified for a certain visit are damaged or lost.

4.4. Study therapy, doses, and dosage regimens of investigational products. Pharmaceutical form, packaging, and labeling of investigational products

4.4.1. Study therapy, doses, and dosage regimens of investigational products

In this study, BCD-085 will be administered to patients in three of four study arms. Patients will receive 40 mg, 80 mg, or 120 mg BCD-085 as SC injections once weekly for the first three weeks (induction regimen) and then once every two weeks (maintenance regimen). Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction

period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period).

For blinding purposes, patients from 40 mg and 80 mg arms will be given two or one SC injection of placebo (1 mL each), respectively.

Patients in the control arm will receive three SC injections of placebo. Placebo to be used has the similar composition for all three arms and contains the same excipients that the BCD-085 dosage form.

Regardless of the arm to which the patient is assigned, injections will be performed by an authorized site medical nurse directly in the study site. Injections can be given to the abdomen, hips, or upper arms. Injections should be given at least 5 cm apart. The overall duration of all three injections should not exceed 15 min from the beginning of the first injection.

4.4.2. Pharmaceutical form, packaging, and labeling of investigational products

The test drug and placebo will have similar packaging differing only by the lot number and shelf life.

4.4.2.1. Test drug

[redacted]

4.4.2.2. Placebo

[redacted]

4.4.2.3. Labeling of investigational products

This study is blind so the investigational products will be labeled the same way.

According to Article 46 of Federal Law 61-FZ "On the Circulation of Medicines" of April 12, 2010 and regulatory requirements of the participating countries, [redacted]

[redacted]

Both primary and secondary package will also have the following labeling: “For Clinical Trials Only”.

The secondary package will also contain the following information: protocol ID, study site number, patient’s ID (entered by the investigator).

4.5. Expected duration of the study and subjects’ participation in the study

The expected duration of the study is 26 months, which includes patients' recruitment (up to 12 months), treatment period, follow-up period, and data collection and statistical processing. It is planned that each subject will participate in the study for up to 18 weeks, including screening (up to 4 weeks), active study phase (10 weeks), and follow-up (4 weeks).

4.6. Study periods

4.6.1 Study schedule (visits and procedures)

The study includes the following periods:

- Screening (Days -28 to 0)
- Treatment period (weeks 1 to 10)
- Follow-up (weeks 11 to 14)

Table 14 lists all the procedures to be performed in the study. All the data obtained during these assessments must be confirmed by the source documents.

Screening/baseline assessment should be performed within 28 days before the estimated date of the first infusion of BCD-085/placebo Prior results may be used for certain screening tests and exams (see section 4.7 for details). At the end of the screening period, the patient should be assessed for the inclusion/exclusion criteria and undergo randomization.

Table 14. Schedule of study visits and procedures.

Visit	Screening	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	# 11	# 12	#13
Week	**Week -4 - Week 0**	**Week 0**	**Week 0[20]**	**Week 0[20]**	**Week 0[20]**	**Week 0[20]**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**
Days	**-28-0**	**1**	**2**	**3**	**4**	**7**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**Any day of the week**
Taking informed consent	+													
Collection of medical history and complaints	+													
Collection of the information about prior/concurrent therapy	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BP, wrist pulse, and body temperature	+	+[21]					+	+	+	+	+	+	+	+
Physical exam (including body weight and height measurements)[22]	+	+					+	+	+	+	+	+	+	+
CBC	+						+				+		+	+
Blood biochemistry[23]	+						+				+		+	+
Coagulation profile	+						+				+		+	+
Tests for HIV, HCV, HBV, syphilis	+[24]													

[20] The visit in person is performed only with a limited number of patients involved in the PK assessment.
[21] BP, pulse, and t° is measured any time before and immediately after the injection of BCD-085/placebo.
[22] The height is measured at screening only.
[23] Alkaline phosphatase is measured at screening only.
[24] Test results for HIV, HCV, HBV, and syphilis obtained within 1 month are valid at screening.

Visit	Screening	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	# 11	# 12	#13
Week	**Week -4 - Week 0**	**Week 0**	**Week 0[20]**	**Week 0[20]**	**Week 0[20]**	**Week 0[20]**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**
Days	**-28-0**	**1**	**2**	**3**	**4**	**7**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**Any day of the week**
Disakintest® [25] or blood sampling for QuantiFERON test[26]	+													
Urinalysis	+						+						+	+
ECG	+						+							+
Chest X-ray (front view)[27]	+													+
Pregnancy test[28]	+													
Checking for eligibility (inclusion/non-inclusion criteria)	+													
Inclusion in the study (randomization and stratification)	+													
Administration of the investigational product		+					+	+	+	+	+	+		
[redacted]														
[redacted]														

[25] If Diaskintest®/QuantiFERON test cannot be performed, the Mantoux test may be performed instead.

[26] QuantiFERON test is recommended if skin tests cannot be performed (skin lesions in the middle of the inside forearm).

[27] Chest fluorography can be used instead of chest X-ray. Screening chest X-ray is not required if the patient had chest X-ray/fluorography/CT/MRI done within 1 month before signing the informed consent form for this study.

[28] Pregnancy test detects hCG in the urine (test strips). Pregnancy test is not required if the patient is at least 2 years postmenopausal or had a uterus or ovary surgery that makes pregnancy impossible.

[redacted]

Visit	Screening	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	# 11	# 12	#13
Week	Week -4 - Week 0	Week 0	Week 0[20]	Week 0[20]	Week 0[20]	Week 0[20]	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14
Days	-28-0	1	2	3	4	7	8	15	29	43	57	71	85	Any day of the week
[redacted]														
Assessment of the area and severity of psoriasis (PASI score)	+								+		+		+	
Assessment of psoriasis severity with sPGA	+								+		+		+	
Calculation of the body surface area affected by psoriasis (BSA)	+								+		+		+	
Assessment of the psoriasis involvement of nails (NAPSI)	+												+	
Taking photos	+								+		+		+	
The patient fills out the VAS for pruritus	+	+					+		+		+		+	
DLQI and SF-36 questionnaires	+								+		+		+	
Assessment the injection pain, VAS		+					+	+	+	+	+	+		
Assessment of injection site reactions		+[32]					+	+	+	+	+	+	+	
Documenting AEs/SAEs	+[33]	+	+	+	+	+	+	+	+	+	+	+	+	+

[redacted]

[32] Twice: Day 1 / Week 0 (4 h and 8 h after the injection of BCD-085/placebo)
[33] At screening, only serious adverse events should be registered.

4.6.2. Procedures by visits

Procedures of the screening period

The screening period starts when the patient signs the informed consent form and lasts for not more than 4 weeks (Days -28 to 0) until the day when the patient is included in the study.

- Check informed consent is taken from the patient
- Take medical history and document any patient complaints
- Collect the information about concomitant treatments (and treatments used within 1 month before inclusion in the study)
- BP, wrist pulse, and body temperature
- Physical exam (including body weight and height measurements)
- Complete blood count[34] (3 mL)
- Bloodbiochemistry[34] (9 mL)
- Coagulation profile (6 mL)
- Tests for HIV, HCV, HBV, and syphilis (12 mL)
- Urinalysis
- ECG
- Chest x-ray / fluorography
- Pregnancy test[35]
- Assessment of the area and severity of psoriasis with PASI
- Assessment of psoriasis severity with sPGA
- Assessment of the body surface area affected by psoriasis (BSA)
- Assessment of psoriasis involvement of nails (NAPSI)
- [redacted]
- The patient fills out the VAS for pruritus
- DLQI and SF-36 questionnaires

[34] At screening, the test can be repeated once, if the first result did not meet the eligibility criteria.
[35] Pregnancy test is required only for women of childbearing potential and does not apply to post-menopausal women.

- TB test[36] (cutaneous Diaskintest® or drawing blood for QuantiFERON test[37] (testing blood plasma for the presence of gamma interferon))
- Checking for eligibility (inclusion/non-inclusion criteria)
- Inclusion in the study (randomization and stratification)
- Documenting SAEs

Total blood volume taken at the visit: 30 mL

Procedures of Visit 1 (Day 1, Week 0):

- Physical exam (including body weight)
- The patient fills out the VAS for pruritus
- [redacted]
- Collecting the information about concurrent therapy
- [redacted]
- Administration of BCD-085/placebo
- Assessment of the injection site pain with VAS (immediately after the injection of BCD-085/placebo)
- BP, pulse, and tº (measured any time before and immediately after the injection of BCD-085)
- [redacted]
- Assessment of the injection site reaction (twice: 4 h and 8 h after the injection of BCD-085/placebo)
- Documenting AEs/SAEs

[36]If Diaskintest®/QuantiFERON test cannot be performed, the Mantoux test can be done instead. The patients with uncertain or positive Mantoux test results are allowed in the study if the following conditions are met: a qualified specialist excluded TB infection (a written report had to be provided) and the chest X-ray exam performed within 1 month before randomization revealed no signs of active TB infection.

[37]QuantiFERON test is recommended if skin tests cannot be performed (skin lesions in the middle of the inside forearm).

[redacted]

Total blood volume taken at the visit: 13 mL (for all patients) [redacted].

Procedures of Visit 2 (Day 2 of Week 0). [redacted]

- [redacted]
- Collection of the information about concurrent therapy
- Documenting AEs/SAEs

[redacted]

Procedures of Visit 3 (Day 3 of Week 0). [redacted]

- [redacted]
- Collection of the information about concurrent therapy
- Documenting AEs/SAEs

[redacted]

Procedures of Visit 4 (Day 4 of Week 0). [redacted]

- [redacted]
- Collection of the information about concurrent therapy
- Documenting AEs/SAEs

[redacted]

Procedures of Visit 5 (Day 7 of Week 0). [redacted]

- [redacted]
- Collection of the information about concurrent therapy
- Documenting AEs/SAEs

[redacted]

Procedures of Visit 6 (Day 1, Week 1) performed 7 days after the first dose of BCD-085/placebo:

- Physical exam (including body weight)
- [redacted]
- Complete blood count (3 mL)
- Blood biochemistry (9 mL)
- Coagulation profile (6 mL)
- Urinalysis
- The patient fills out the VAS for pruritus
- 2nd administration of BCD-085/placebo
- Assessment of the injection site pain with VAS (immediately after the injection of BCD-085/placebo)
- Blood pressure, heart rate and body temperature (immediately after dosing)
- ECG
- Collection of the information about concurrent therapy
- Assessment of injection site reactions
- Documenting AEs/SAEs

Total blood volume taken at the visit: [redacted] 18 mL for all other patients.

Procedures of Visit 7 (Day 1, Week 2) performed 7 days after the 2nd dose of BCD-085/placebo:

- Physical exam (including body weight)
- [redacted]
- 3rd administration of BCD-085/placebo
- Assessment of the injection site pain with VAS (immediately after the injection of BCD-085/placebo)

[redacted]

- Blood pressure, heart rate and body temperature (immediately after dosing)
- Collection of the information about concurrent therapy
- Assessment of injection site reactions
- Documenting AEs/SAEs

[redacted]

Procedures of Visit 8 (Day 1, Week 4) performed 14 days after the 3rd dose of BCD-085/placebo:

- Physical exam (including body weight)
- Assessment of the area and severity of psoriasis with PASI
- Assessment of psoriasis severity with sPGA
- Assessment of the body surface area affected by psoriasis (BSA)
- [redacted]
- The patient fills out the VAS for pruritus
- DLQI and SF-36 questionnaires
- [redacted]
- 4th administration of BCD-085/placebo
- Assessment of the injection site pain with VAS (immediately after the injection of BCD-085/placebo)
- Blood pressure, heart rate and body temperature (immediately after dosing)
- Collection of the information about concurrent therapy
- Assessment of injection site reactions
- Documenting AEs/SAEs

[redacted]

Visit 9 (Day 1, Week 6) performed 14 days after the 4th dose of BCD-085/placebo:

- Physical exam (including body weight and height measurements)
- [redacted]

[redacted]

- 5th administration of BCD-085/placebo
- Assessment of the injection site pain with VAS (immediately after the injection of BCD-085/placebo)
- Blood pressure, heart rate and body temperature (immediately after dosing)
- Collection of the information about concurrent therapy
- Assessment of injection site reactions
- Documenting AEs/SAEs

[redacted]

Visit 10 (Day 1, Week 8) performed 14 days after the 5th dose of BCD-085/placebo:

- Physical exam (including body weight)
- Assessment of the area and severity of psoriasis with PASI
- Assessment of psoriasis severity with sPGA
- Assessment of the body surface area affected by psoriasis (BSA)
- [redacted]
- The patient fills out the VAS for pruritus
- DLQI and SF-36 questionnaires
- Complete blood count (3 mL)
- Blood biochemistry (9 mL)
- Coagulation profile (6 mL)
- Blood sampling for immunogenicity assay (8 mL)
- [redacted]
- 6th administration of BCD-085/placebo
- Assessment of the injection site pain with VAS (immediately after the injection of BCD-085/placebo)
- Blood pressure, heart rate and body temperature (immediately after dosing)
- Collection of the information about concurrent therapy
- Assessment of injection site reactions
- Documenting AEs/SAEs

[redacted]

Total blood volume taken at the visit: [redacted] 26 mL [redacted].

Visit 11 (Day 1, Week 10) performed 14 days after the 6th dose of BCD-085/placebo:

- Physical exam (including body weight)
- [redacted]
- 7th administration of BCD-085/placebo
- Assessment of the injection site pain with VAS (immediately after the injection of BCD-085/placebo)
- Blood pressure, heart rate and body temperature (immediately after dosing)
- Collection of the information about concurrent therapy
- Assessment of injection site reactions
- Documenting AEs/SAEs

[redacted]

Visit 12 (Day 1, Week 12) performed 14 days after the 7th dose of BCD-085/placebo:

- Physical exam (including body weight)
- Assessment of the area and severity of psoriasis with PASI
- Assessment of psoriasis severity with sPGA
- Assessment of the body surface area affected by psoriasis (BSA)
- Assessment of psoriasis involvement of nails (NAPSI)
- [redacted]
- The patient fills out the VAS for pruritus
- [redacted]
- Blood pressure, wrist pulse, and body temperature
- Complete blood count (3 mL)
- Blood biochemistry (9 mL)
- [redacted]
- Coagulation profile (6 mL)
- Urinalysis

[redacted]

- DLQI and SF-36 questionnaires
- Collection of the information about concurrent therapy
- Assessment of injection site reactions
- Documenting AEs/SAEs

Total blood volume taken at the visit: [redacted] 23 mL [redacted].

Visit 13 (any day of Week 14), performed 28-34 days after the 7th dose of BCD-085/placebo:

- Physical exam (including body weight)
- [redacted]
- Complete blood count (3 mL)
- Blood biochemistry (9 mL)
- Coagulation profile (6 mL)
- [redacted]
- Chest x-ray / fluorography
- Urinalysis
- ECG
- Blood pressure, wrist pulse, and body temperature
- Collection of the information about concurrent therapy
- Documenting AEs/SAEs
- Completion of the study by the patient

Total blood volume taken at the visit: 26 mL (for all patients) [redacted]

During unscheduled visits, the investigator must document AEs/SAEs. Other procedures are on the discretion of the investigator and must be entered in the CRF as comments to an unscheduled visit.

4.7. Description of individual study procedures

All scheduled clinical and laboratory procedures and timings are listed in Table 15.

[redacted]

Table 15. Clinical and laboratory investigations in the study.

Test	Tested variable	Frequency	Where the test is performed
Physical examination	• Standard medical examination by organs and systems	×10: 1. Screening 2. Day 1 / Week 0 3. Day 1 / Week 1 4. Day 1 / Week 2 5. Day 1 / Week 4 6. Day 1 / Week 6 7. Day 1 / Week 8 8. Day 1 / Week 10 9. Day 1 / Week 12 Any day of Week 14	Study site
Height	• Height, cm	×1: At baseline (screening)	Study site
Body weight	• Body weight, kg	×10: 1. Screening 2. Day 1/ Week 0 3. Day 1 / Week 1 4. Day 1 / Week 2 5. Day 1 / Week 4 6. Day 1 / Week 6 7. Day 1 / Week 8 8. Day 1 / Week 10 9. Day 1 / Week 12 10. Any day of Week 14	Study site
Vital signs	• BP, mm Hg • Wrist pulse, bpm • Body temperature (axillary), °C	×11: 1. Screening 2. Day 1 / Week 0 (×2: any time before and immediately after the injection of BCD-085/placebo). 3. Day 1 / Week 1 4. Day 1 / Week 2 5. Day 1 / Week 4 6. Day 1 / Week 6 7. Day 1 / Week 8 8. Day 1 / Week 10 9. Day 1 / Week 12 10. Any day of Week 14	Study site

Test	Tested variable	Frequency	Where the test is performed
CBC	• Hemoglobin (g/L) • Hematocrit (%) • RBC (× 10^{12}/ L) • Platelets (× 10^{9}/ L) • WBC (× 10^{9}/ L) • ANC (× 10^{9}/ L) • Lymphocytes (× 10^{9}/ L) • Monocytes (×10^{9}/ L) • ESR, Westergen (mm/h) (blood volume is 3 mL)	×5: 1. Screening 2. Day 1 / Week 1 3. Day 1 / Week 8 4. Day 1 / Week 12 5. Any day of Week 14	Study site or central lab (depending on the equipment of the study site)
Blood biochemistry	• Glucose (mmol/L) • Bilirubin total (µmol/L) • Bilirubin indirect, • ALT (U/L) • AST (U/L) • GGT (U/L) • LDH (U/L) • AlkPh (U/L)[46], • Total protein (g/L) • Creatinine (µmol/L). (blood volume is 9 mL)	×5: 1. Screening 2. Day 1 / Week 1 3. Day 1 / Week 8 4. Day 1 / Week 12 5. Any day of Week 14	Study site or central lab (depending on the equipment of the study site)
Coagulation profile	• Prothrombin ratio (%) • APTT (sec) (blood volume is 6 mL)	×5: 1. Screening 2. Day 1 / Week 1 3. Day 1 / Week 8 4. Day 1 / Week 12 5. Any day of Week 14	Study site or central lab (depending on the equipment of the study site)
Serology[47]	• HIV Ag/Ab Combo, • anti-HbCor (total IgM and IgG), • HBsAg, • anti-HbCor (total IgM and IgG), • Microprecipitaion + direct hemagglutination to T. pallidum. (blood volume is 10 mL)	×1: At baseline (screening)	Study site or central lab (depending on the equipment of the study site)

[46] Alkaline phosphatase is measured at screening only.
[47] HIV, HBV, HCV, and syphilis test results were considered valid for screening if they were obtained within 1 month before signing the ICF and if the test fully met the requirements of this Protocol.

Test	Tested variable	Frequency	Where the test is performed
	Additional tests: • Anti- HbCor (IgM) • Anti- HbCor (IgG) • Quantitative PCR for HCV RNA • Quantitative PCR for HBV DNA (blood volume is 10 mL)		
Urinalysis	• General properties (color, clarity, specific gravity, pH, protein, glucose); • Urinary sediment microscopy (epithelium, erythrocytes, leukocytes, cylinders, bacteria, salts).	×4: 1. Screening 2. Day 1 / Week 1 3. Day 1 / Week 12 4. Any day of Week 14	Study site
Pregnancy test	• HCG in the urea	×1: At baseline (screening)	Study site
Instrumental examinations	• 12-lead ECG	×3: 1. Screening 2. Day 1 / Week 1 3. Any day of Week 14	Study site
	• Chest X-ray / fluorography (front view)[48]	×2: 1. At baseline (screening) 2. Any day of Week 14	Study site
[redacted]	[redacted]	[redacted]	JSC BIOCAD, separate subdivision (central laboratory)

[48] The test is not required if the patient provides results of chest X-ray/fluorography/CT/MRI performed within 1 month before inclusion in the study.

Test	Tested variable	Frequency	Where the test is performed
		[redacted]	
[redacted]	[redacted]	[redacted]	JSC BIOCAD, separate

Test	Tested variable	Frequency	Where the test is performed
		[redacted]	subdivision (central laboratory)
[redacted]	[redacted]	[redacted]	JSC BIOCAD, separate sub-division (central laboratory)
Skin test for TB or drawing blood specimens for QuantiFERON test[49]	• Diaskintest®[50] or QuantiFERON test	×1: At baseline (screening)	Study site
Pruritus assessed by the patient	• 0-100 mm VAS, where 0 refers to no itch and 100 refers to unbearable itch	×6: 1. Screening 2. Day 1 / Week 0 3. Day 1 / Week 1 4. Day 1 / Week 4 5. Day 1 / Week 8 6. Day 1 / Week 12	Study site
Assessment of the area and severity of psoriasis (PASI)	• Total score reflecting the severity and area of psoriasis	×4: 1. Screening 2. Day 1 / Week 4 3. Day 1 / Week 8 4. Day 1 / Week 12	Study site
Assessment of psoriasis severity with sPGA	• Severity of psoriasis symptoms	×4: 1. Screening 2. Day 1 / Week 4 3. Day 1 / Week 8 4. Day 1 / Week 12	Study site
Assessment of the body surface area affected by psoriasis (BSA)	• % Affected area	×4: 1. Screening 2. Day 1 / Week 4 3. Day 1 / Week 8 4. Day 1 / Week 12	Study site

[49]QuantiFERON test is recommended if skin tests cannot be performed (skin lesions in the middle of the inside forearm).

[50]If Diaskintest®/QuantiFERON test cannot be performed, the Mantoux test may be performed instead.

Test	Tested variable	Frequency	Where the test is performed
Assessment of psoriasis involvement of nails (NAPSI)	• Score for nail matrix and nail bed involvement	×2: 1. Screening 2. Day 1 / Week 12	Study site
Taking photos	N/A	×4: 1. Screening 2. Day 1 / Week 4 3. Day 1 / Week 8 4. Day 1 / Week 12	Study site
Assessment the injection pain, VAS	• Pain assessed by the patient, VAS	×7: 1. Day 1 / Week 0 2. Day 1 / Week 1 3. Day 1 / Week 2 4. Day 1 / Week 4 5. Day 1 / Week 6 6. Day 1 / Week 8 7. Day 1 / Week 10	Study site
Assessment of injection site reactions	• Any administration site reaction (yes/no)	×9: 1-2. Day 1 / Week 0 (4 h and 8 h after the injection of BCD-085/placebo) 3. Day 1 / Week 1 4. Day 1 / Week 2 5. Day 1 / Week 4 6. Day 1 / Week 6 7. Day 1 / Week 8 8. Day 1 / Week 10 9. Day 1 / Week 12	Study site
Assessment of the quality of life	SF-36 and DLQI questionnaires	×4: 1. Screening 2. Day 1 / Week 4 3. Day 1 / Week 8 4. Day 1 / Week 12	Study site

4.7.1. History taking, complaints, demographics

The following data should be recorded at screening:

– Date of birth

– Gender

– Age

- Ethnic origin
- Reproductive potential [use of contraception (specify which measures), menopause state, its duration, sterilization, if applicable]
- Medical history (infections in the past, chronic infectious-inflammatory diseases, a history of tuberculosis, contacts with a patient with tuberculosis, other chronic skin inflammatory disorders, immunodeficiency, concomitant conditions) with the onset/resolution dates (if applicable)
- Medical history (approximate date of psoriasis onset, area and severity of psoriasis before and at screening, effects of treatment)
- Medication history:

A) Specify all medications that the patient has received for the treatment of psoriasis, with doses, dosing regimens, therapy duration, and efficacy of each medication, in the opinion of the Investigator. If the medication was discontinued, specify the reason.

B) Specify any medications that the patient has been taking within 30 days before screening. Specify dose, dosage regimen, treatment duration, and the reason for discontinuation (if applicable). Medications for the treatment of psoriasis that the patient uses now of has been using within 30 days before screening must be recorded in the *"Medication Therapy for psoriasis"* section.

4.7.2. Physical examination

The following organs and systems must be assessed during the physical exam:

- Height (at screening only)
- Body weight (at screening and before each injection of BCD-085/placebo)
- Skin and mucosa (visual examination, describe all pathological changes that are not due to psoriasis)
- Lymphatic nodes (visual examination, palpation)
- Ear/nose/throat, respiratory organs (examination, lung auscultation)
- Cardiovascular system (heart auscultation, examination of major vessels area)
- GI (examination, palpation of abdominal area)
- Spleen size (palpation, percussion)
- Spleen size (palpation, percussion)
- Urogenital system (kidney punch, palpation of kidney and bladder area)

- Nervous system (meningeal signs, focal neurological signs)
- Mental health (signs of depressive disorder, suicidal ideation, acute psychotic disorder)

Examination must be performed at screening, Visit 1 (Day 1 of Week 0), Visit 6 (Day 1 of Week 1), Visit 7 (Day 1 of Week 2), Visit 8 (Day 1 of Week 4), Visit 9 (Day 1 of Week 6), Visit 10 (Day 1 of Week 8), Visit 11 (Day 1 of Week 10), Visit 12 (Day 1 of Week 12), and Visit 13 (any day of Week 14).

4.7.3. Vital signs

Vital signs include axillary body temperature (ºC), blood pressure (on one arm, mm Hg), and wrist pulse.

Vital signs must be checked at screening, Visit 1 (Day 1 of Week 0, twice - any time before and immediately after the injection), Visit 6 (Day 1 of Week 1), Visit 7 (Day 1 of Week 2), Visit 8 (Day 1 of Week 4), Visit 9 (Day 1 of Week 6), Visit 10 (Day 1 of Week 8), Visit 11 (Day 1 of Week 10), Visit 12 (Day 1 of Week 12), and Visit 13 (any day of Week 14).

4.7.4. Laboratory tests

Laboratory tests include CBC, blood biochemistry, coagulation pattern, [redacted], and urinalysis. In addition, markers of HIV, hepatitis B and C, and syphilis will be determined at screening.

4.7.4.1. CBC

CBC is performed at fasting in accordance with the standard procedure (fasting means at least 8 hours without food). This study includes the following CBC parameters:

- Hemoglobin (g/L)
- RBC ($\times 10^{12}$/L)
- WBC ($\times 10^{9}$/L)
- Platelets ($\times 10^{9}$/L)
- Neutrophils ($\times 10^{9}$/L)
- Lymphocytes ($\times 10^{9}$/L)
- Monocytes ($\times 10^{9}$/L)
- ESR (mm/h) must be measured by Westergren method only. Any other method for ESR is not allowed.

The volume of blood taken: **3 mL**.

Blood sampling is performed using standard procedures.

CBC is done at screening, Visit 6 (Day 1 of Week 1), Visit 10 (Day 1 of Week 8), Visit 12 (Day 1 of Week 12), and Visit 13 (any day of Week 14).

4.7.4.2. Blood biochemistry

Blood biochemistry is performed according to the standard procedure at a fasting state (8 hours after the last meal including any sweat or alcohol drinks).

The following variables are to be evaluated:

- Glucose(mmol/L)
- Bilirubin total(μmol/L)
- Bilirubin indirect (μmol/L)
- ALT (U/L)
- AST (U/L)
- GGT (U/L)
- LDH (U/L)
- Alkaline phosphatase [51] (U/L)
- Total protein (g/L)
- Creatinine (μmol/L)

Volume of blood taken: **9 mL**.

Blood sampling is performed using standard procedures.

Blood biochemistry is done at screening, Visit 6 (Day 1 of Week 1), Visit 10 (Day 1 of Week 8), Visit 12 (Day 1 of Week 12), and Visit 13 (any day of Week 14). Alkaline phosphatase is measured at screening only.

4.7.4.3. Coagulation pattern

Coagulation pattern is tested according to the standard procedure at fasting state (8 hours after the last meal). This study includes the following parameters:

Prothrombin ratio (%)

APTT (sec)

[51] Alkaline phosphatase is measured at screening only.

The volume of blood taken: **6 mL**.

Blood sampling is performed using standard procedures.

Coagulation profile is done at screening, Visit 6 (Day 1 of Week 1), Visit 10 (Day 1 of Week 8), Visit 12 (Day 1 of Week 12), and Visit 13 (any day of Week 14).

4.7.4.4. Serology

The test for HIV-infection means a qualitative assessment for HIV p24 antigen and HIV Ag/Ab Combo in serum or plasma.

The test for syphilis is performed as a microprecipitation and direct hemagglutination assay (T. pallidum). Other tests can also be used.

The presence/absence of HBV is assessed by testing the serum or plasma for HbsAg and for total anti-HBcor (IgG + IgM). If the HbsAg test results are positive, the patient cannot be enrolled in the study.

If the patient is negative for HbsAg and positive for HBcor, a qualitative PCR for HBV DNA must be performed together with the test for anti-HBcor (IgG and IgM) and a consultation with an infectious disease specialist.

Patients with positive anti-HBcor Ab results are eligible for the study if all of the following conditions are met:

- Results of the qualitative PCR for HBV DNA are negative
- Results of the test for anti-HBcor (IgG and IgM) are negative
- No biochemistry abnormalities are found
- Infectious disease specialists confirm the absence of hepatitis B (medical records must be sent to the Sponsor and retained in the source documents and Investigator's File)
- The Sponsor approves inclusion of this patient.

The presence/absence of hepatitis C is assessed based on the results of the test for anti-HCV antibodies (total IgM + IgG). If the patient is positive for anti-HCV antibodies, a qualitative PCR for HCV RNA and a consultation with an infectious disease specialist are required.

Patients with positive anti-HCV Ab results are eligible for the study if all of the following conditions are met:

- Results of the qualitative PCR for HCV RNA are negative
- No biochemistry abnormalities are found

- Infectious disease specialists confirm the absence of hepatitis C (medical records must be sent to the Sponsor and retained in the source documents and Investigator's File)
- The Sponsor approves inclusion of this patient.

All these tests are performed using routine procedures of the study site or central laboratory. To prepare for the tests, the patient should fast for 8 hours before blood drawing.

The test is performed once, at screening[52].

The volume of blood taken: **12 mL**.

4.7.4.5. Urinalysis

Urine sampling and urinalysis will be performed using standard procedures. Urinalysis included general properties of urine (color, clarity, specific gravity, pH, protein, and glucose) and urinary sediment microscopy (epithelium, erythrocytes, leukocytes, cylinders, bacteria, salts).

Urinalysis is done at screening, Visit 6 (Day 1 of Week 1), Visit 10 (Day 1 of Week 8), Visit 12 (Day 1 of Week 12), and Visit 13 (any day of Week 14).

4.7.5. ECG

A 12-lead ECG is recorded according to a standard procedure.

ECG is taken at screening, Visit 6 (Day 1 of Week 1), and Visit 13 (any day of Week 14).

4.7.6. Tuberculosis diagnostics

This study will accept results of the Diaskintest® or QuantiFERON assays obtained with the standard procedures. Only Diaskintest® or QuantiFERON results obtained during the screening will be accepted. Diaskintest® or QuantiFERON test and their interpretations must be performed by a certified healthcare professional.

The test is performed once, at screening.

4.7.6.1. Skin test for tuberculosis

Diaskintest® is a cutaneous TB test in this study. Diaskintest® is an intra-skin diagnostic test with a recombinant protein containing two antigens (ESAT6 and CFP10) of *Micobacterium*

[52]Test results for HIV, HCV, HBV, and syphilis obtained within 1 month are valid at screening.

tuberculosis and *Micobacterium bovis*, virulent strains of mycobacteria. The procedure and of Diaskintest® and results assessment are similar to those of the Mantoux test (PPD-L). The test is done with a thin needle, intradermally, into the middle third of the antebrachium. After 72 hours, the physician or nurse evaluates the response by measuring the transverse (with reference to the brachium axis) size of hyperemia and infiltrate (papula) in mm with a transparent ruler. Hyperemia is taken into account only if no infiltrate is seen. The following responses for the test can be seen (source http://www.diaskintest.ru/page_2.html):

- Negative: no infiltrate or hyperemia. A "prick reaction" of up to 2 mm may be seen
- Doubtful: hyperemia without infiltrate
- Positive: infiltrate (papula) of any size.

If the test result is doubtful, the patient can be enrolled after a negative QuantiFERON result is obtained or if additional requirements specified in section 4.7.6.3 are met.

The Diaskintest® is a mandatory procedure for all enrolled patients. The only exception are patients who have contraindications to skin tests (e.g., patients have skin lesions in the middle of the inside forearm). Such patients should take the QuantiFERON test (plasma test for gamma immunoglobulins).

The Diaskintest® is performed at a local TB dispensary or at the study site the qualified staff is available (materials will be provided by JSC BIOCAD).

4.7.6.2. Plasma test for gamma interferon (QuantiFERON test)

QuantiFERON test is recommended if skin tests cannot be performed (the patient has contraindications for skin tests, e.g., skin lesions in the middle of the inside forearm) or is the results of the Diaskintest® are uncertain. The QuantiFERON test allows evaluating plasma levels of the specific gamma interferon to confirm or exclude the tuberculosis infection.

The procedure of the QuantiFERON test:

Blood should be taken in the morning strictly at fasting state (or not less than 8 hours after the last food intake) into three vacuum test tubes from a QuantiFERON Assay Kit (positive control, negative control, test), with 1 mL of blood placed in each tube. The tubes with the blood must be kept at room temperature (+17°C to +25°C). Do not refrigerate or freeze the blood samples. The tubes in the QuantiFERON Tubes pack must be delivered to the central laboratory within 10 hours after the blood was drawn (the overall transportation time must not exceed 12

hours). The samples are shipped in an insulated container (tubes placed vertically) at a temperature from +17 to +25°C.

At the laboratory, the tubes are incubated for 16-24 hours. During the incubation, lymphocytes recognize mycobacterial antigens. This recognition process includes the production of gamma interferon. The central laboratory performs ELISA to check the plasma for gamma interferon produced as an immune response to the antigens.

For the QuantiFERON test, use only tubes from the QuantiFERON Assay Kit because each its tube contains a specific antigen. Do not use any tubes with the same colors but not from the QuantiFERON Assay Kit.

Interpretation of QuantiFERON test results. Three options are available: Positive, negative, and doubtful. Doubtful results are possible due to the sensitivity to the tuberculosis antigen. If the test result is doubtful, the patient can be enrolled only if additional requirements specified in section 4.7.6.3 are met.

4.7.6.3. Additional methods for tuberculosis diagnostics

Patients with doubtful QuantiFERON results can be included in the study if all of the following requirements are met: A TB specialist excludes the TB infection (appropriate records must be sent to the Sponsor and retained in the source documents and Investigator's File); the patient has no signs of active TB as confirmed by the chest X-ray performed any time within 1 month before randomization.

If the Diaskintest®/QuantiFERON test could not be performed, the Mantoux test is allowed instead. The patients with uncertain or positive Mantoux test results are allowed in the study if the following conditions are met: A TB specialist excludes the TB infection (appropriate records must be sent to the Sponsor and retained in the source documents and Investigator's File); the patient has no signs of active TB as confirmed by the chest X-ray performed any time within 1 month before randomization.

4.7.7. Chest x-ray / fluorography

Chest X-ray is performed with standard procedures of the study site to exclude tuberculosis or other lung diseases. Images are taken in the front view. If necessary, the Sponsor's representative may request the images (if the subject develops active TB while in the study).

The test is done at screening and on Visit 13 (Day 1 of Week 14).

Chest fluorography may be performed instead of the chest X-ray. Screening chest X-ray is not required if the patient has results of the chest X-ray/fluorography/CT/MRI performed within 1 month before signing the informed consent.

4.7.8. PASI and BSA assessment

The area and severity of skin signs of psoriasis can be assessed with a PASI score. The form presented in Table 16 is used to assess the PASI score.

Table 16. PSORIASIS AREA AND SEVERITY INDEX (PASI)

The degree of the symptom:
0-absent, 1–slight, 2–moderate, 3–severe, 4–extremely severe

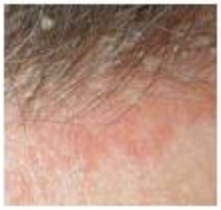
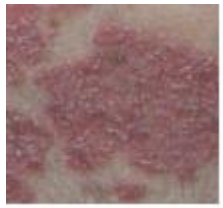
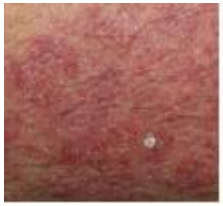
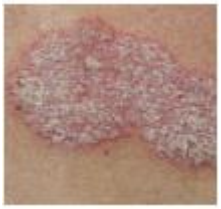
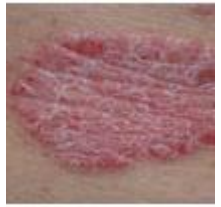
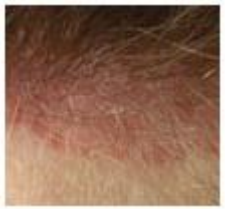
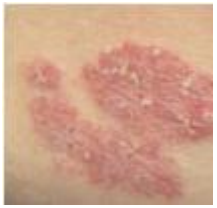
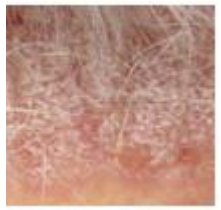
1	**Erythema**	Head and neck	Trunk	Upper extremities	Lower extremities
		0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
2	**Induration**	Head and neck	Trunk	Upper extremities	Lower extremities
		0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
3	**Desquamation**	Head and neck	Trunk	Upper extremities	Lower extremities
		0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
4	**Total**				

Affected area, %

5	**0: 0%, 1: < 10%, 2: from 10 to 29%, 3: from 30 to 49%, 4: from 50 to 69%, 5: from 70 to 89%, 6: from 90 to 100%**				
6	**Affected area**				
7	**Multiply the value in line 4 by the value in line 6**				
8	**Weight of section**	×0.1	×0.3	×0.2	×0.4
9	**Multiply the value in line 7 by the value in line 8**				
Total score (sum of the scores from all columns)					

Each symptom (erythema, induration, and desquamation) is assessed with a 4-score scale ranging from 0 (no symptoms) to 4 (max severity), separately for the skin of head and neck, body, arms and legs (lines 1-3). Assess the skin area mostly affected by the symptom.

Use the pictures below for PASI scoring (http://www.unhwamedi.com/Newsub02/Newsub05_a08.php).

Parameter	None	Mild	Moderate	Severe	Extremely severe
Erythema					
Score	0	1	2	3	4
Induration					
Score	0	1	2	3	4
Desquamation					
Score	0	1	2	3	4

After that, scores are summarized (line 4).

The area of skin affected by psoriasis is then estimated for each area. The area of skin affected by psoriasis is estimated with the palm rule. The area of the human palm without fingers corresponds to about 1% of all his/her skin. It is assumed that the skin of the head and neck corresponds to 10% of all skin area, trunk – to 30%, arms – to 20%, and legs – to 40%. Correspondingly, one palm corresponds to 10% of the skin on the head, 3.3% of the skin on the trunk, 5% of the skin on the upper extremities, and 2.5% of the skin on the lower extremities.

To estimate the affected area from sections in scores, compare the affected area (%) from each section to line 5 of Table 16 and note the score in line 6.

After that, multiply the value in line 7 by weight of respective section (0.1 for the head, 0.2 for upper extremities, 0.3 for body and 0.4 for lower extremities).

Summarize values in line 9 to receive the PASI score, which can vary from 0 (no rashes) to 72 (the most severe psoriatic process).

The PASI score is calculated automatically when the investigator enters the following data in the eCRF: severity of erythema, induration, and desquamation in the evaluated body areas and the body surface area affected by psoriasis. The total PASI score and severity degree of individual symptoms of several localizations (lines 1-4 of Table 16) must be recorded in the source documents

The body surface area affected by psoriasis is determined by the investigator at study visits and recorded in source documents and eCRF as a total body surface affected by psoriasis (%). The “palm” rule is used for assessment.

Assessment is performed at screening, on Visit 8 (Day 1 of Week 4), Visit 10 (Day 1 of Week 8), and Visit 12 (Day 1 of Week 12).

4.7.9. The sPGA assessment

The severity of psoriasis is evaluated by the investigator using the scale explained below. The scale is used to assess the psoriatic lesions in a certain patient. Within each area, the severity is estimated by three criteria (induration, desquamation, and erythema). Not all three criteria may be present. Induration is considered the most resistant symptom, while the presence of desquamation or erythema can vary. In this case, the index is a sum of scores for infiltration of lesions and one of the prevailing criteria (erythema or desquamation).

Table 18. Static Physician's Global Assessment (sPGA).

Score	Category	Description
0	No signs of psoriasis	Plaque induration = 0 (no elevation over normal skin) Desquamation = 0 (no scaling) Erythema = 0 (residual post-inflammatory pigmentation)
1	Minimal	Plaque induration = +/- (possible but difficult to ascertain whether there is a slight elevation above normal skin) Desquamation = +/- (surface dryness with some white coloration) Erythema = moderate (definite red coloration)
2	Moderate	Plaque induration = slight (slight but definite elevation, typically edges are indistinct or sloped) Desquamation = fine (fine scale partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Low	Plaque induration = moderate (moderate elevation with rough or sloped edges) Desquamation = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque induration = pronounced (pronounced elevation typically with hard or sharp edges) Desquamation = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very severe	Plaque induration = very marked (very marked elevation typically with hard sharp edges) Desquamation = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

The investigator determines the sPGA score at each visit and records it in the source documents and eCRF.

Assessment is performed at screening, on Visit 8 (Day 1 of Week 4), Visit 10 (Day 1 of Week 8), and Visit 12 (Day 1 of Week 12).

4.7.10. Quality of life assessment

The quality of life in the study subjects will be assessed with the DLQI and SF-36 questionnaires (in Russian for Russian-speaking patients and in English for all other patients).

The patient should fill in the questionnaires during the visit at the study site. The investigator must ensure that the patients fill out the questionnaires at the beginning of the visit before any of the study procedures.

Table 19. The DLQI questionnaire.

No.	Question	Very much / very often	A lot / often	A little	Not at all / do not know
1	Over the last week, how itchy, sore, painful or stinging has your skin been?	3	2	1	0
2	Over the last week, how embarrassed or self-conscious have you been because of your skin?	3	2	1	0
3	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	3	2	1	0
4	Over the last week, how much has your skin influenced the clothes you wear?	3	2	1	0
5	Over the last week, how much has your skin affected any social or leisure activities?	3	2	1	0
6	Over the last week, how much has your skin made it difficult for you to do any sport?	3	2	1	0
7	Over the last week, has your skin prevented you from working or studying?	3	2	1	0
8	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	3	2	1	0
9	Over the last week, how much has your skin caused any sexual difficulties?	3	2	1	0
10	Over the last week, how much of a problem has the treatment for your skin been, for example by taking up time or money, making you less focused on your work or family?	3	2	1	0
Total score					

Each question was assessed using a 3-point scale, where score 3 means "very much", score 2 means "a lot", score 1 - "a little", and score 0 - "not at all". Question 7: the "Yes" answer scores 3; the "No" answer scores 0. If more than two questions are left unanswered, the questionnaire is considered invalid. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

The SF-36 questionnaire is presented in Appendix 1 to the Protocol.

All questionnaires must be filled out only by the patient or his/her legal representative. DLQI and SF-36 questionnaires must not be given to patients for completing at home. They must by filled at the study center on the visit day. Completed questionnaires should be stored in the Investigator's File.

Assessment is performed at screening, on Visit 8 (Day 1 of Week 4), Visit 10 (Day 1 of Week 8), and Visit 12 (Day 1 of Week 12).

4.7.11. Psoriasis involvement of nails (NAPSI)

Matrix involvement (pitting, leukonychia, red spots in the lunula, and nail plate crumbling) and/or nail bed involvement (onycholysis, nail bed hyperkeratosis, hemorrhages, "oil drops") are assessed. The whole nail (the most affected one) is divided into quadrants. In each quadrant, the severity of nail matrix and nail bed involvement is assigned a score from 0 to 4. The sum of these two indexes (symptoms of the nail bed and matrix affection) is the total NAPSI score.

The higher is NAPSI, the more severe are pathological changes in nails. The maximum score (8) corresponds to the total involvement of the nail plate.

Table 20. Nail psoriasis severity index (NAPSI).

Right hand: Nail matrix involvement *(pitting, leukonychia, red spots, crumbling)* 0 — no symptoms, 1 — symptoms are present in one nail quadrant, 2 — symptoms are present in two nail quadrants, 3 — symptoms are present in three nail quadrants, 4 — symptoms are present in four nail quadrants.	
Nail of the little finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the ring finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the third finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the index finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the thumb	0 □ 1 □ 2 □ 3 □ 4□
Right hand: Nail bed involvement *(onycholysis, subungual hyperkeratosis, hemorrhages, "oil drops")* 0 — no symptoms, 1 — symptoms are present in one nail quadrant, 2 — symptoms are present in two nail quadrants, 3 — symptoms are present in three nail quadrants, 4 — symptoms are present in four nail quadrants.	
Nail of the little finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the ring finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the third finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the index finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the thumb	0 □ 1 □ 2 □ 3 □ 4□

Left hand: Nail matrix involvement *(pitting, leukonychia, red spots, crumbling)* 0 — no symptoms, 1 — symptoms are present in one nail quadrant, 2 — symptoms are present in two nail quadrants, 3 — symptoms are present in three nail quadrants, 4 — symptoms are present in four nail quadrants.	
Nail of the little finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the ring finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the third finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the index finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the thumb	0 □ 1 □ 2 □ 3 □ 4□
Left hand: Nail bed involvement *(onycholysis, subungual hyperkeratosis, hemorrhages, "oil drops")* 0 — no symptoms, 1 — symptoms are present in one nail quadrant, 2 — symptoms are present in two nail quadrants, 3 — symptoms are present in three nail quadrants, 4 — symptoms are present in four nail quadrants.	
Nail of the little finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the ring finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the third finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the index finger	0 □ 1 □ 2 □ 3 □ 4□
Nail of the thumb	0 □ 1 □ 2 □ 3 □ 4□

The NAPSI is used to assign a score to each nail, which can vary from 0 to 8. All 8 components can be assessed for one target nail; in this case, the index can vary from 0 to 32. In this study, nail involvement will be assessed only for hands, so the total index of all nails can be from 0 to 80 (only hands). The Investigator should perform a complete assessment of hand NAPSI with questionnaires for recording scores for each nail. The total score is calculated automatically when data from the questionnaire are recorded in the eCRF. The score should be also recorded in the source documents.

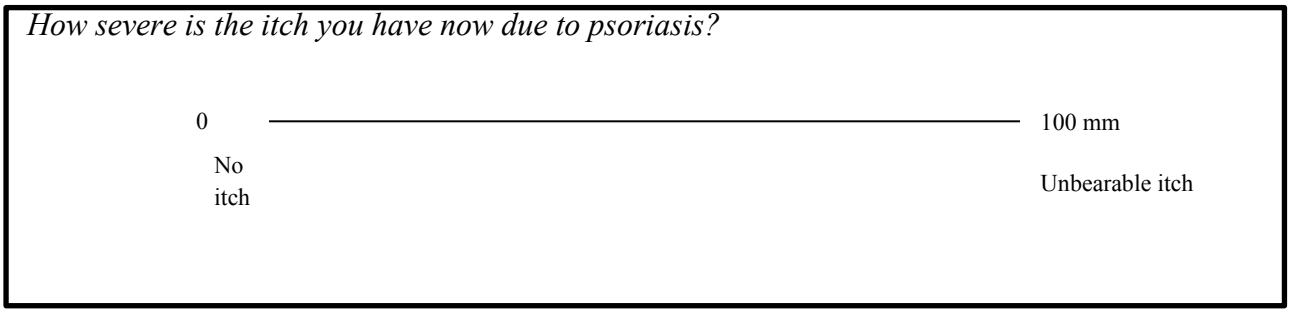
The test is done at screening and on Visit 12 (Day 1 of Week 12).

4.7.12 Patient's assessment of pruritus

The patient will assess itch severity with a visual analog scale, from 0 (no itch) to 100 mm (unbearable itch). It is required that the patient fills the scale while at the study center during

the visit. The completed VAS is stored in the Investigator's File; the score is recorded in the patient's source documents. The Investigator records VAS results in the eCRF.

Figure 6. An example of the visual analog scale for itch assessment.



The test is done at screening, on Visit 1 (Day 1 of Week 0), Visit 6 (Day 1 of Week 1), Visit 8 (Day 1 of Week 4), Visit 10 (Day 1 of Week 8), and Visit 12 (any day of Week 12).

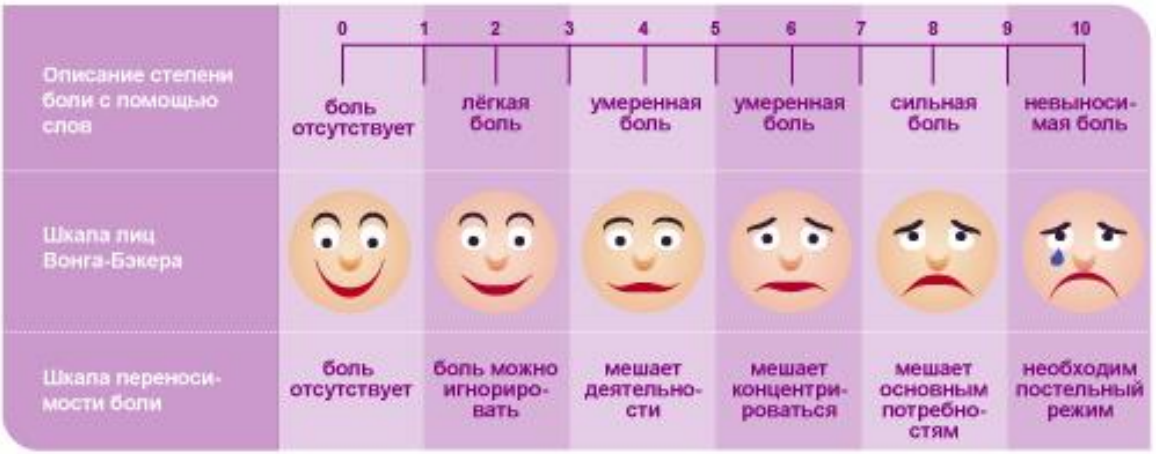
4.7.13 Assessment the injection pain

The study subject assesses how painful was the injection immediately after the injection and by filling out a special 10-score VAS (see below). It is required that the patient fills the scale while at the study center during the visit. Since the study drug is given as three injections, the patient will be asked to assess the most painful one.

The completed VAS must be kept in the Investigator's File; the score is recorded in the patient's source documents. The investigator records the VAS score in the eCRF.

Figure 7. Visual analogue scale for patient's assessment of pain.

Instructions: This scale shows how painful was the injection. The score 0 refers to no pain, the score10 refers to the highest, almost unbearable pain.



Verbal description of pain	No pain	Mild pain	Moderate pain	Moderate pain	Severe pain	Worst pain possible
Wong-Baker Faces						
Tolerance scale	No pain	Can be ignored	Interferes with tasks	Interferes with concentration	Interferes with basic needs	Bedrest required

The assessment is performed on Visit 1 (Day 1 of Week 0), Visit 6 (Day 1 of Week 1), Visit 7 (Day 1 of Week 2), Visit 8 (Day 1 of Week 4), Visit 9 (Day 1 of Week 6), Visit 10 (Day 1 of Week 8), and Visit 11 (Day 1 of Week 10).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.7.18. Total blood volume taken during the study

Table 21 gives the estimated volume of blood to be taken at each visit and during the entire study.

Table 21. The volume of blood to be taken from each subject in the study.

Visit	Laboratory tests (frequency/blood taken per 1 sample)	Total blood volume
Screening	• CBC (3 mL) • Biochemistry (9 mL) • Coagulation profile (6 mL) • Blood tests for markers of hepatites, HIV, syphilis (12 mL) • QuantiFERON test[53] (3 mL)	30 mL (33 mL[54])
Visit 1 (Day 1/Week 0)	[redacted]	[redacted]

[53] QuantiFERON test is recommended if skin tests cannot be performed (skin lesions in the middle of the inside forearm).
[54] If the QuantiFERON test is done.

Visit	Laboratory tests (frequency/blood taken per 1 sample)	Total blood volume
Visit 2 (Day 2/Week 0)	• [redacted]	[redacted]
Visit 3 (Day 3/Week 0)	•	
Visit 4 (Day 4/Week 0)	•	
Visit 5 (Day 7/Week 0)	•	
Visit 6 (Day 1/Week 1)	• CBC (3 mL) • Biochemistry (9 mL) • Coagulation profile (6 mL) •	18 mL [redacted]
Visit 7 (Day 1/Week 2)	•	6 mL (patients from the PK population)
Visit 8 (Day 1/Week 4)	•	6 mL (patients from the PK population)
Visit 9 (Day 1/Week 6)	•	6 mL (patients from the PK population)
Visit 10 (Day 1/Week 8)	• • CBC (3 mL) • Biochemistry (9 mL) • Coagulation profile (6 mL)	26 mL [redacted]
Visit 11 (Day 1/Week 10)	[redacted]	
Visit 12 (Day 1/Week 12)	• • CBC (3 mL) • Biochemistry (9 mL) • Coagulation profile (6 mL) •	23 mL [redacted]
Visit 13 - any day at Week 14	• CBC (3 mL) • Biochemistry (9 mL) • Coagulation profile (6 mL) • •	26 mL [redacted]
Total blood volume taken from one subject over the entire study		**136 mL (139 mL[54])**
[redacted]		

[redacted]

[redacted]

4.7.20. Data entering to eCRF

The principal investigator and the study team members will be provided logins and passwords to enter the eCRF system.

Electronic CRF should be completed within 5 working days after the visit. All screening data should be entered at once after the screening.

In the eCRF system, patients are identified only with their unique subject IDs. No screening IDs can ever be used in eCRFs.

The screen failure data are not required to be entered in the eCRF.

4.8. Stop rules and criteria for premature withdrawal for study subjects, study periods, and study as a whole

4.8.1. Stop rules for study as a whole

The study may be stopped in the following situations:

1. By the decision of JSC BIOCAD due to safety reasons, ethical considerations, compliance issues, or any other reasons.
2. By the decision of LECs or regulatory authorities.

4.8.2. Criteria for premature withdrawal of study subjects

The patient will be withdrawn from the study in the following circumstances:

1. A major violation of inclusion/exclusion criteria is revealed after the patient was enrolled

[redacted]

in the study (withdrawn by the decision of JSC BIOCAD)[54]

2. The patient recalls his/her consent to participate in the study
3. The patient develops adverse events or serious adverse events, laboratory abnormalities or concomitant conditions that, in the investigator's opinion, make further participation in the study impossible, dangerous or non-beneficial regarding patient's well-being/safety
4. The patient misses more than 2 infusions (in this case, patient's removal must be approved by JSC BIOCAD, refer to section 6.5. *Compliance Assessment*) or misses 2 successive visits or 3 visits in total, or the patient regularly (3 times or more) violates the timing of the scheduled visits
5. The patient gets pregnant. If pregnancy is suspected, the urine test for HCG must be performed. If the test shows a positive result, the patient must be withdrawn from the study (follow-up procedures are described in section 5.4)
6. The patient has a major depressive disorder, suicidal ideation or attempts
7. The study is terminated by the decision of JSC BIOCAD, local ethics committees, or regulatory authorities
8. The patient uses medications prohibited by the Protocol
9. The patient dies.

The investigator must inform JSC BIOCAD within 24 h about a patient's premature withdrawal and specify the reason.

If the subject discontinues the study, an Early Withdrawal Form in the CRF should be filled out. The follow-up procedures for the discontinued subjects are described in section 5.4 *Procedures by visits*.

Subjects who were prematurely withdrawn due to safety reasons are not to be replaced.

See section 11.5 for further details. *Study termination*.

4.9. Drug accountability

The investigator is responsible for the test drug/placebo accountability at the trial site. Throughout the study, the investigator must ensure proper accountability of the investigational product as required by regulatory authorities. The investigator must maintain accurate records regarding the receipt of the investigational product from JSC BIOCAD, its dispensing to study subjects and return to JSC BIOCAD.

[54] Violations of inclusion/exclusion criteria justified by the Investigator and approved by the Sponsor cannot be a reason to withdraw the patient from the study.

When the investigator or the pharmacist receives the investigational product, he/she should check the delivery, sign and date a receipt form and documentation provided by JSC BIOCAD, and return it to JSC BIOCAD. A copy of this documentation must be stored in the Investigator File.

The amount of investigational product delivered to the study site must be recorded in the receipt form provided by JSC BIOCAD. This form will be used as an investigational product accountability record.

Accurate accountability records should be available to the Monitor during each monitoring visit. Drug accountability records should include:

- Confirmation of delivery of the investigational product to the study site
- Inventory at the study site
- Use of investigational product by each study subject
- Return of unused drug product to JSC BIOCAD.

Records should include dates, amounts, batch numbers, and expiry dates of the investigational product (if applicable). The investigator must maintain accountability records to ensure that:

- Study subjects get the investigational product at doses specified by the Protocol/Amendment
- The total amount of the investigational product provided by JSC BIOCAD is accurately checked and delivered undamaged.

Unused investigational product must not be used for any other purpose except this study.

The Monitor from JSC BIOCAD will regularly inspect accountability records.

4.9.1. Handling of investigational products

The test drug/placebo delivered to the study site should be stored 2°C to 8°C, protected from light. All medicinal products supplied by the Sponsor must be stored in a limited access area. Only the principal investigator, co-investigators, and an authorized representative of the site administration will have access to the storage area.

The investigational product may be stored only at the study sites authorized for this clinical trial. The investigator must ensure safe storage of the investigational drug to prevent loss, theft, or improper environmental conditions (temperature) specified by the Sponsor and described in the Investigator Brochure. The investigator must maintain a temperature log.

4.10. Procedure for keeping and unblinding randomization codes

As this study is double-blind, the study product and placebo will be identified only by the patient-specific lot number. JSC BIOCAD will prepare a few envelop kits with therapy arm codes (i.e. with lot numbers corresponding to the test product/placebo). One of these envelop kits will be stored at JSC BIOCAD; another will be given to the principal investigator of every study center and stored in the Investigator's File.

The investigator is allowed to unblind the treatment only in case of an emergency. The investigator must exercise his/her best efforts to prevent the loss or unblinding of study codes when unnecessary.

Treatment can be unblinded only in case of an emergency when this is necessary to give an appropriate treatment to the patient and ensure his/her well-being. If a medical situation that requires unblinding occurs, the principal investigator must contact a representative from JSC BIOCAD: medical expert, pharmacovigilance officer, or clinical study manager (for contact details see the title page), specify unblinding reasons and obtain consent to this procedure. If JSC BIOCAD approves unblinding, the investigator unblinds the code, records this fact in the source document, and notifies the clinical study manager by phone or e-mail.

All patients participating in the study will receive Subject ID cards containing the protocol code, study site number, investigator’s contact information, contact information of the BIOCAD’s responsible medical officer and pharmacovigilance officer (available 24 h daily). Patients should know that they should have their study subject’s cards all the time with them and notice medical personnel of any other medical facility about their participation in this clinical study. If necessary (for example, to administer another medicinal product), a physician of another medical facility (other than the study center) can contact the Investigator to discuss benefit or possible risks related to concomitant therapy.

4.11. Data entered directly into CRF (i.e. no prior written or electronic record of data) and considered as source data

All data entered to the CRF must be recorded in the source documentation.

In this study, no data will be entered directly to the CRFs without prior entering to the source documents.

5. ELIGIBILITY AND EXCLUSION OF STUDY SUBJECTS

5.1. Inclusion criteria

1. Signed informed consent form
2. Age of 18 to 65 years inclusive
3. Plaque-type psoriasis, moderate to severe, stable for at least 6 months at the time of inclusion in the study (i.e. no changes in the morphological signs of psoriasis, no significant worsening or exacerbations were seen during this period, as judged by the investigator)
4. Patients received at least one course of phototherapy or systemic therapy[55] for psoriasis or are candidates[56] for such treatment according to the investigator
5. At screening, body surface area (BSA) affected by plague psoriasis of 10% or greater, PASI score of 12 or greater, and an sPGA score of 3 or greater
6. Treatment failure or unbearable toxicity with /contraindications for TNFα inhibitors or other biologics (monoclonal antibodies or their fragments) administered for at least 3 months. If such patient is included in the study, the treatment must be stopped at least 12 calendar days before signing the informed consent
7. Laboratory values at screening:
   - Hemoglobin ≥ 9 g/dL (90 g/dL)
   - WBC ≥ 3 000/μL (3.0×10^9/L)
   - Platelets ≥ 100 000/μL (100×10^9/L)
   - Neutrophils ≥ 2 000/μL (2.0×10^9/L)
   - AST, ALT, and alkaline phosphatase ≤ 2.5 ULN
   - Serum creatinine < 176.8 μmol/L (2.0 mg/dL)
   - The negative test result for serologic and virologic markers for active/latent hepatitis B (HBV) and hepatitis C (HCV).
8. Negative pregnancy urine test in female subjects (no test is required in women who are post-menopausal for at least 2 years and in surgically sterile women)
9. No history of tuberculosis

[55]Systemic therapy refers to any non-biologics (methotrexate, cyclosporine, acitretin, etc.), or biologics (TNF inhibitors, anticytokine drugs, anti-CD20 drugs, etc.)

[56]BCD-085 is planned to be used as either first- or second-line treatment, so the study involves treatment-naive patients along with those who failed to respond to systemic or phototherapy.

10. Negative Diaskintest® results[57] or negative QuantiFERON test results[58]
11. Patients with uncertain Diaskintest® results are eligible for the study if they show negative results with QuantiFERON test. Patients with uncertain QuantiFERON test are eligible for the study if a qualified specialist confirms no TB infection (a written report must be provided) and the chest X-ray exam performed within 1 month before randomization reveals no signs of active TB infection
12. No history of or current alcohol or drug abuse at baseline
13. The patient must be able to follow the Protocol procedures (in the investigator's opinion)
14. Patients of childbearing potential and their partners with preserved reproductive function must consent to practice reliable contraceptive starting from 2 weeks before inclusion in the study and for 4 weeks after the last dose of screening to 4 weeks after the last dose of the study drug. This requirement does not apply to you if you have undergone surgical sterilization. Reliable contraception means one barrier method in combination with one of the following: spermicides or intrauterine device / oral contraceptives used by the subject's partner.

5.2. Exclusion criteria

1. Baseline erythrodermic, pustular, and guttate psoriasis, drug-induced psoriasis, or any other skin diseases (e.g. eczema) that can affect/complicate the assessment of psoriasis treatment.
2. Concomitant therapy:
   - Prior use of monoclonal antibodies targeting IL17 or its receptor
   - Prior use of two or more TNFα-inhibiting monoclonal antibodies or their fragments
   - Prior use of two or more monoclonal antibodies against other targets
   - Prior use of monoclonal antibodies within 12 weeks before signing the informed consent
   - Oral glucocorticoids >10 mg (equivalent to prednisolone) during 4 weeks prior to signing the informed consent and throughout entire screening period; oral glucocorticoids ≤10 mg/day if the dose was not stable for 4 weeks prior to signing the informed consent and through the entire screening period

[57] If Diaskintest®/QuantiFERON test cannot be performed, the Mantoux test can be done instead. The patients with uncertain or positive Mantoux test results are allowed in the study if the following conditions are met: a qualified specialist excluded TB infection (a written report must be provided) and the chest X-ray exam performed within 1 month before randomization revealed no signs of active TB infection.

[58] QuantiFERON test is recommended if skin tests cannot be performed (skin lesions in the middle of the inside forearm).

- Use of systemic non-biologics including methotrexate, sulfasalazine, cyclosporine, and acitretin within 4 weeks before randomization. This was an exclusion criterion if doses of said drugs were not stable for 4 weeks before signing the informed consent and during the entire screening period. If prior systemic therapy with non-biologics was stopped due to any reasons, the screening period could be extended up to 8 weeks during which no new non-biologics were allowed
- Phototherapy (including selective UCB phototherapy and PUVA therapy) within 4 weeks before randomization
- Live or attenuated vaccines administered at any time during 8 weeks before screening

3. Recurring, chromic or any other active infection if the investigator considers that the study drug can harm the patient

4. Documented HIV-infection or a history of a severe immunodeficiency of any origin

5. Positive screening results for Hbs-antigen, hepatitis B core antibodies (anti-HBc Ab)[59] and/or hepatitis C antibodies[60]

6. Current/history of tuberculosis

7. Current or a history of herpes zoster[61]

8. Positive results of microprecipitation reaction together with positive TPHA assay results at screening

9. Concurrent diseases ongoing at screening that may increase the risk of adverse events during the study or affect the evaluation of psoriasis symptoms (mask, enhance or alter the symptoms of psoriasis, or cause clinical or laboratory signs/symptoms similar to those of psoriasis):

- active inflammatory diseases or aggravation of chronic inflammatory diseases other than psoriasis
- Stable angina class III-IV, unstable angina or a history of myocardial infarction within 1 year before signing the informed consent
- Moderate to severe cardiac insufficiency (NYHA classes III and IV)

[59]Patients with positive anti-HBc Ab results are eligible for the study if all of the following conditions are met: negative qualitative PCR results for HBV DNA (this test is performed only if anti-HBV antibodies were detected); blood test results available for anti-HBc IgG and anti-HBC IgM; no abnormalities found in blood biochemistry; medical infections specialist provides a documented conclusion that the patient has no HBV; and the Sponsor approves enrollment of this particular patient.

[60]Patients with positive anti-HBC Ab results are eligible for the study if all of the following conditions are met: negative qualitative PCR results for HCV DNA (this test is performed only if anti-HBC antibodies were detected); no abnormalities found in blood biochemistry; medical infections specialist provides a documented conclusion that the patient has no HCV; and the Sponsor approves enrollment of this particular patient.

[61] No additional test for antibodies to varicella-zoster virus are required. The decision is based on clinical signs and medical history.

- Severe treatment-resistant hypertension[62]
- A history of atopic asthma or angioedema;
- Moderate to severe respiratory failure, COPD grade 3/4
- Decompensated diabetes mellitus, decompensated hypothyroidism, decompensated hyperthyroidism
- Systemic autoimmune diseases (including lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Crohn/s disease, ulcerative colitis, systemic sclerosis, inflammatory myopathies, mixed connective tissue disease[63], intersection syndrome, etc.)
- Any other concurrent diseases (including but not limited to metabolic, hematologic, hepatic, renal, pulmonary, neurological, endocrine, cardiac, gastrointestinal, and infectious diseases) that may affect the course of psoriasis, affect the assessment of signs/symptoms of psoriasis, or put patients using the study treatment at additional risk

10. Malignancies within the past 5 years (other than adequately treated (cured) squamous or basal cell carcinoma, cervical cancer *in situ* or ductal carcinoma *in situ*)
11. Known severe allergies (anaphylaxis or multiple drug allergy)
12. Known allergy or intolerance to monoclonal antibody drugs (murine, chimeric, humanized, or human) or any other components of the study drug
13. Major surgery within 30 days before the screening, or a major surgery being scheduled at any time during the study
14. Severe infections (including those requiring hospitalization or parenteral antibacterial/antimycotic/antiprotozoal treatment) within 6 months before the first dose of the study drug;
15. Systemic use of antibacterial/antimycotic/antiprotozoal drugs within 2 months before the first dose of the study drug
16. More than 4 episodes of respiratory infection within 6 months before screening
17. A history of epileptic attacks or seizures
18. The patient cannot stop phototherapy (including UVB and PUVA therapy) for psoriasis
19. Any concurrent diseases during which, in the investigator's opinion, the study treatment can harm the patient
20. Pregnancy, breastfeeding or planning for pregnancy while participating in the study

[62]Treatment-resistant arterial hypertension is defined as blood pressure above the target range despite the concurrent use of three anti hypertensive drugs of different classes, including a diuretic, and non-medication methods (salt-free diet, controlled physical exercise).

[63] Signs/symptoms of psoriatic arthritis are not considered an exclusion criterion.

21. Any psychiatric disorders, including a history of major depression and/or suicidal thoughts that can, in the investigator's opinion, put the patient at risk or affect patient's ability to follow the study protocol
22. Patients with the existence of or history of abuse of recreational drugs, prescription drugs, alcohol, or any other psychoactive substances
23. Participation in any other clinical study within 3 months before screening or simultaneous participation in other clinical studies
24. Patients who were randomized to this study and then discontinued the study due to any reasons (i.e. patients who met all other inclusion/exclusion criteria), were not re-enrolled in this study.

5.3. Withdrawal criteria

The patient will be withdrawn from the study in the following circumstances:

1. A major violation of inclusion/exclusion criteria is revealed after the patient was enrolled in the study (withdrawn by the decision of JSC BIOCAD)[64]
2. The patient recalls his/her consent to participate in the study
3. The patient develops adverse events or serious adverse events, laboratory abnormalities or concomitant conditions that, in the investigator's opinion, make further participation in the study impossible, dangerous or non-beneficial regarding patient's well-being/safety
4. The patient misses more than 2 infusions (in this case, patient's removal must be approved by JSC BIOCAD, refer to section 6.5. *Compliance Assessment*) or misses 2 successive visits or 3 visits in total, or the patient regularly (3 times or more) violates the timing of the scheduled visits
5. If the patient gets pregnant. In case of a suspicion for pregnancy, the urine test for HCG should be performed. In case of a positive result, the patient is to be withdrawn from the study
6. The patient has a major depressive disorder, suicidal ideation or attempts
7. The study is terminated by the decision of JSC BIOCAD, local ethics committees, or regulatory authorities
8. The patient uses medications prohibited by the Protocol
9. The patient dies.

The investigator must inform JSC BIOCAD within 24 h about a patient's premature withdrawal and specify the reason.

[64] Violations of inclusion/exclusion criteria justified by the Investigator and approved by the Sponsor cannot be a reason to withdraw the patient from the study.

5.4. Follow-up of subjects withdrawn from the study or subjects who discontinued the study treatment but remain in the study for follow-up

5.4.1. Follow-up of patients who received at least one dose of BCD-085/placebo

The following should be done if the patient who received at least one injection of BCD-085/placebo discontinues the study early:

- The Early Withdrawal Visit should be performed at the day of withdrawal with the Early Withdrawal Form being filled out. AEs/SAEs must be registered during this visit, while the amount of other examinations is to the discretion of the investigator.

If the subject discontinues the study due to an AE/SAE, the investigator should conduct further treatment and follow-up after the Early Withdrawal Visit in accordance with the study site standards for the treatment of a certain AE/SAE. The patient should be followed up until **the AE or SAE resolves completely**.

The woman who discontinues the trial because of pregnancy should be monitored through the entire pregnancy and for 6 months after delivery to evaluate the mother's and child's health. Information on pregnancy course and outcome should be recorded in the source documents (after the patient provides her consent). During the whole period of pregnancy, the investigator in collaboration with the attending Ob/Gyn specialist should monitor the patient's overall health, the course of pregnancy, and laboratory values including ultrasound. When the child is born, the investigator together with the attending pediatrician should monitor the newborn for 6 months evaluating the child's clinical status and the laboratory/instrumental findings.

Information regarding the health state of all dropouts should be recorded in their source documentation and CRFs.

5.4.2. Follow-up of subjects who did not receive a single dose of BCBD-085/placebo

If the subject discontinues the study before dosing, the Early Withdrawal Form should be filled out on the day of withdrawal. Non-dosed patients are followed-up only if they discontinue the study because of AEs/SAEs. In this case, the follow up is performed according to the study site standards.

If the subject withdraws from the study due to any reason after receiving a dose of the test drug/comparator, his/her data will be included in the analysis. If the subject withdraws from the study before dosing, his/her information will be removed from the analysis.

6. TREATMENT OF STUDY SUBJECTS

6.1. Study therapy

In this study, BCD-085 will be administered to patients in three of four study arms. Patients will receive 40 mg, 80 mg, or 120 mg BCD-085 as SC injections once weekly for the first three weeks (induction regimen) and then once every two weeks (maintenance regimen). Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction period), Day 1 of Week 4, Day 1 of Week 6, Day 1 of Week 8, and Day 1 of Week 10 (maintenance period).

For blinding purposes, patients from 40 mg and 80 mg arms will receive two or one SC injection of placebo (1 mL each), respectively.

Patients in the control arm will receive 3 SC injections of placebo (each injection is 1.0 mL). Placebo to be used has the similar composition for all three arms and contains the same excipients that the BCD-085 dosage form.

Regardless of the arm to which the patient is assigned, injections will be performed by an authorized site medical nurse directly in the study site. Injections can be given to the abdomen, hips, or upper arms. Injections should be given at least 5 cm apart.

During the entire study period, patients are not allowed to use phototherapy (UV-B), photochemotherapy (PUVA), biologics other than BCD-085, and live or attenuated vaccines.

The patients can use systemic non-biologic therapies (methotrexate, sulfasalazine, chlorambucil, leflunomide, cyclosporine A, azathioprine, aromatic retinoids (acetretin), and glucocorticoids (> 10 mg of prednisolone equivalent per day) if their dose was stable for 4 weeks before signing the informed consent and through the entire screening period) Patients are not allowed to change their systemic non-biologic treatment during the study, increase the dose, or add any new medications of this category. Patients are allowed to discontinue systemic non-biologic therapies only if he/she has any life- or health-threatening adverse effects due to this treatment. Any modifications of the dosing regimen or dose reduction for systemic non-biologic therapy can be made only after reconciliation with the Sponsor.

The patients may use topical glucocorticoids on the face, underarm, and genitals. The patients may use topical moisturizing products, emollients, oils or salicylic acid-based products if necessary. The patients should discontinue all local skin products (medications or cosmetics) 24 hours before the planned PASI assessment.

6.1.1. Preparation of the investigational products for administration and administration procedure

6.1.1.1. Test drug and placebo

Injections will be given at the study site by the investigator or an authorized nurse (a member of the study team).

Since several SC injections were given at once, it was preferred to use the same area with two injection sites being at least 5 cm apart. Multiple injections should be performed within 15 minutes. The time for PK blood drawing is counted from the last injection.

6.1.2. Adjustment and discontinuation of study therapy

6.1.2.1. Dose modification and discontinuation of the study drug

No dose modifications for the study drug are allowed in this study. If the investigator decides that further treatment / participation in the study does not meet the best patient's interests, this patient may be withdrawn from the study.

6.1.1.1.1. Follow-up for toxicity

In case of temporary or permanent therapy discontinuation, the patient should be followed up until the resolution or stabilization of the event. If the therapy is suspended for more than 14 days, it should be discontinued permanently. However, if the investigator and the Medical Expert believe that the patient who discontinued the drug for more than 14 days may get benefit from the therapy, the study treatment may be continued.

To reveal AEs and SAEs, all patients will be followed up for 28 days from the last dose of BCD-085/placebo.

6.1.3. Overdose

6.1.3.1. Overdose with study drug

No overdose events has been described with BCD-085. Effects of BCD-085 injected at single doses higher than 3 mg/kg are not known. If an overdose is registered in this study, and the patient develops some adverse events related, in the investigator's opinion, to the overdose, further treatment should be given at the discretion of the attending physician. No antidote is available, so appropriate symptomatic treatment should be applied.

6.2. Concomitant therapy, medications allowed and prohibited by the Protocol

6.2.1. Allowed concomitant therapy

The patients can use systemic non-biologic therapies (methotrexate, sulfasalazine, chlorambucil, leflunomide, cyclosporine A, azathioprine, aromatic retinoids (acetretin), and glucocorticoids (> 10 mg of prednisolone equivalent per day) if their dose was stable for 4 weeks before signing the informed consent and through the entire screening period) Patients are not allowed to change their systemic non-biologic treatment during the study, increase the dose, or add any new medications of this category. Patients are allowed to discontinue systemic non-

biologic therapies only if he/she has any life- or health-threatening adverse effects due to this treatment. Any modifications of the dosing regimen or dose reduction for systemic non-biologic therapy can be made only after reconciliation with the Sponsor.

The patients may use topical glucocorticoids on the face, underarm, and genitals. The patients may use topical moisturizing products, emollients, oils or salicylic acid-based products if necessary. The patients should discontinue all local skin products (medications or cosmetics) 24 hours before the planned PASI assessment.

6.2.2. Prohibited concomitant therapy

Treatments prohibited in this study:

- ✓ Biologics (including other anti-IL-17 monoclonal antibodies, TNFα inhibitors, anti-cytokine agents, anti-CD20 agents, etc.)
- ✓ New systemic non-biologics or dose modification for already used systemic non-biologics[65]
- ✓ Systemic[66] glucocorticoids (except for < 10 mg/day of prednisolone equivalent if the dose was stable for 4 weeks before signing the informed consent)
- ✓ Phototherapy [including selective phototherapy (UVB) and photochemotherapy (PUVA)]
- ✓ Any unauthorized products other than BCD-085
- ✓ Opioid analgesics
- ✓ Vaccines.

The study participant who received or needs any prohibited treatment must be withdrawn from the study.

6.3. Compliance with study procedures

In this study, the information will be documented about each administration of the investigational product, doses, and intervals between the study visits.

The Clinical Research Associate (CRA) will inspect the study documentation during monitoring visits and upon completion of the study.

[65]No dose increase was allowed for systemic non-biologics. Any modifications of the dosing regimen or dose reduction for systemic non-biologic therapy can be made only after reconciliation with the Sponsor.

[66] Doses > 10 mg were allowed in the active study period if glucocorticoids were used parenterally to manage emergencies such as angioedema, anaphylactic shock, and other types of shock.

6.3.1. Compliance assessment

Non-compliance criteria (the patient must be removed from the study):

- The patient misses more than 2 injections of the study drug (removal has to be reconciled with JSC BIOCAD)

- The patient misses >2 sequential visits or a total of 3 visits in the study

- The patient regularly violates the visit schedule (>3 violations)

- During the first month of treatment, all patients except for those included in the PK population are allowed to re-schedule the visit within 7 days for any reasons (if re-scheduling the visit when the test drug/placebo is to be injected, all subsequent visits must be re-scheduled accordingly).

- For patients in the PK population, visits 1-6 can be re-scheduled within 7 days only due to AEs/SAEs; visits 7 and 8 can be re-scheduled within 7 days due to any reasons. If the visit during which BCD-085/placebo is to be given is re-scheduled, all subsequent visits must be re-scheduled accordingly.

- Visit 9 and subsequent visits are allowed for re-scheduling within 14 days due to any reason. If the visit during which BCD-085/placebo is to be given is re-scheduled, subsequent visits must re-scheduled accordingly.

7. EFFICACY EVALUATION

7.1 List of efficacy variables

7.1.1. Definition of variables

The patient is considered a PASI75 responder if the PASI score improves by 75% from baseline. PASI50 and PASI90 responders are defined in the same way.

7.1.2. Efficacy endpoints

Primary endpoints

- The proportion of patients in each study arm who achieved a PASI 75 at Week 12 of treatment.

7.1.3. Secondary endpoints

- The proportion of patients in each study arm who achieved a PASI 75 at weeks 4 and 8 of treatment
- The proportion of patients in each study arm who achieved a PASI 50/90 at weeks 4, 8, and 12 of treatment
- The relative PASI score improvement from baseline at weeks 4, 8, and 12, by study arms
- The relative BSA improvement from baseline at weeks 4, 8, and 12, by study arms
- The relative NAPSI improvement from baseline at weeks 4, 8, and 12, by study arms
- The mean change from baseline in the intensity of pruritus measured by VAS (0-100 mm) at weeks 1, 4, 8, and 12, by study arms
- The proportion of patients in each study arm who achieved an sPGA score 0 or 1 at weeks 4, 8, and 12 relative to baseline
- The mean change from baseline in the QoL score in each study arm (assessed using the DLQI and SF-36 scales) at weeks 4, 8, and 12.

7.2 Methods and timeframes for assessment, documenting, and analysis of immunogenicity variables

7.2.1 Timeframes for analysis of efficacy variables

The efficacy analysis by the primary endpoint (PASI75) will be performed after **12 weeks** of blinded therapy with BCD-085/placebo.

The timing of the efficacy assessment with the secondary endpoints is specified in section 7.1. *List of efficacy variables*.

7.2.2 Methods and timeframes for assessment and documenting of efficacy variables

Per protocol, the efficacy analysis is to include all patients who received at least one dose of BCD-085/placebo and who attended at least one visit next visit. If no data are available at Week 12, the data from the last assessment are to be used (last-observation-carried-forward method). In addition, these patients should be considered non-responders and analyzed separately.

8. SAFETY ASSESSMENT

8.1 List of safety endpoints

8.1.1 Definitions

8.1.1.1. Adverse events

Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product: from treatment initiation through 28 days after patient withdrawal from the clinical study.

8.1.1.2. Serious adverse events

Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or its prolongation
- Results in persistent or significant incapacitation or disability
- Is a congenital anomaly or birth defect.

In case of any uncertainty whether the event meets the seriousness criteria or not, it should be treated as as a serious adverse event.

An immediate risk of death from a reported event is considered **life threatening**. A life-threatening event does not include an adverse event that, had it occurred in a more severe form, might have caused death, but is not associated with an immediate risk of death in the form it occurred. For example, hepatitis resolved without signs of hepatic insufficiency will not be considered life threatening in spite of the fact that more severe hepatitis can lead to fatal outcome. Similarly, an allergic reaction resulting in face angioedema will not be considered life threatening, although larynx angioedema, allergic bronchospasm or anaphylaxis can lead to fatal outcome.

Hospitalization is an official admission to the hospital. Hospitalization or its prolongation is a criterion of AE seriousness; however, hospitalization itself is not a serious adverse event. Hospitalization or its prolongation not associated with an AE should not be reported by the

investigator as a serious adverse event. This is applicable (including but not limited) to the following cases:

- Hospitalization or prolongation of existing hospitalization is necessary to perform procedures required by the Protocol.
- Hospitalization or prolongation of existing hospitalization is a part of routine procedures in this study site (for example, stent removal after a surgery). An appropriate confirmation should be kept in a study file.
- Hospitalization due to a pre-existing condition, which did not aggravate.

Disability is a significant impairment of the patient's ability to live a normal life.

Other reportable information. Certain information not considered an SAE must be recorded, presented in the report, and followed up as an SAE. This includes:

- The use of the investigational product during pregnancy. If the pregnancy is confirmed, the study therapy should be discontinued immediately.
- The use of the investigational product during breast-feeding, regardless of AE development.
- An overdose of the study drug as defined in the Protocol, whether or not it was associated with an AE.
- Unintentional or accidental use of the investigational product, whether or not considered related to an AE.
- Medication errors whether or not considered related to an AE (including confusion or possible confusion during the administration of investigational products).
- Death whether or not associated with an AE.

8.1.1.3. Unexpected adverse events

The unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

8.1.2. Safety endpoints

- The proportion of patients who develop SAEs
- The proportion of patients who develop AEs
- The proportion of patients who develop administration site reactions

- The proportion of patients who develop grade 3/4 AEs/SAEs
- The proportion of patients who discontinued the study due to AEs/SAEs.

8.2. Methods and timeframes for assessment, documenting and analysis of safety variables

8.2.1. Timeframes for analysis of safety variables

The safety endpoints will be analyzed upon completion of the dosing with BCD-085/placebo and follow-up.

8.2.2. Methods and timeframes for assessment and documenting of safety variables

The safety analysis will include all patients who received at least one dose of the investigational product. Additionally, the SAE analysis will include all randomized patients starting from the ICF signing and until the end of their participation in the study.

Safety will be analyzed based on the information about

- AEs/SAEs;
- Physical examination findings and vital signs
- CBC and biochemistry results, urinalysis results, and coagulation pattern.
- ECG.

The frequency of these procedures is specified in section 4.6.1 *Study schedule (visits and procedures)*. AEs/SAEs will be recorded in accordance with the guide provided by the Sponsor.

The investigator is responsible for recording adverse events in the clinical study.

AEs must be captured starting from the first dose of the investigational product and through 4 weeks after the last dose. AEs related to the protocol procedures must be recorded from the moment the subject signed the ICF. SAEs must be captured from the moment the patient signed the ICF and through 4 weeks after the last dose of the investigational product. The study investigator can report SAEs that occurred after the required follow-up if he/she considers them related to the investigational product or study procedures.

The study investigator must document non-serious AEs in the source documents and in the CRF, and present them to the CRA at the next monitoring visit. SAEs must be reported to the Sponsor immediately (**within 24 hours**). Reports must be submitted to the Sponsor immediately (within 24 hours) by fax [redacted] put “To Pharmacovigilance Officer” in the subject field).

The investigator should receive a receipt/delivery confirmation. Information regarding unexpected adverse reactions must be presented to the CRA at the next scheduled visit.

8.3 Requirements for reports. Documenting and reporting AEs and completing AE Report Forms

8.3.1. Documenting AEs/SAEs

At every visit, a record must be made whether or not any AEs occurred during the period from the previous visit. Any adverse event reported for a patient since he/she signed the ICF must be recorded in source documents and in an Adverse Event Report Form (in the CRF). AEs will be documented in accordance with the Manual provided by the Sponsor.

AEs should be recorded and numbered consecutively as they occur. Each AE is reported in an *AE Reporting Form*. Rules for reporting AE/SAE are described in details in the Sponsor's guide.

Adverse events must be recorded regardless of their seriousness and causal relationship with the study therapy. If an adverse event re-emerges, it must be recorded as a new AE and assigned a new number.

Laboratory/vital sign abnormalities

Laboratory/vital sign abnormalities considered to be adverse events (assessed as clinically meaningful, including those of CTCAE 4.03 grade 1, inducing clinical symptoms or complaints requiring concomitant therapy or changes in study therapy) should be recorded in the CRF, *Adverse Events* section. It is preferable to specify diagnosis rather than individual symptoms (for example, anemia instead of reduced hemoglobin). Laboratory abnormalities meeting the criteria of adverse events should be followed up until they return to a normal or adequate explanation is obtained.

8.3.2. AE/SAE reporting

The AE Report Form should be filled out during the study visit (or the investigator can do it later the same day), except for data not available/not known at that moment. All sections of the form must be filled out. If the data are not available, the following should be entered: "Data not available" or "N/A". However, all actions should be taken to receive all necessary data on emerging adverse events.

The following information is recorded in source documents and the AE Report Form of the CRF:

- AE No. as it occurred
- Visit No.
- A brief description of the AE
- Seriousness (yes/no)
- Seriousness criterion
- CTCAE 4.03 grade
- Onset date
- Date of resolution (return to normal or baseline)
- Outcome
- Actions taken due to the AE
- Causal relationship with the study drug (BCD-085/placebo)
- Comments specifying any clinically relevant (in the investigator's opinion) information related to AE development or therapy.

If a medication therapy is administered, its components should be described in section "Concomitant therapy" of the CRF, with a notice that a medication was used to manage the AE.

Columns *Grade*, *Outcome*, *Measures*, and *Causal Relationship* should be filled using digital codes explained in the *Notes* section. If the investigator considers an AE to be an SAE, he/she must fill out an SAE Report Form in addition to an AE Report From (printed copies).

One SAE Report Form is filled out for one SAE. If the AE remains unresolved at the next visit, the checkbox in AE section of the eCRF should be ticked for the corresponding visit and marked as "unresolved". In this case, a new SAE Report Form should be filled out marked as "Follow-up".

The SAE Report Form must contain the following information:

1) Study information:
   - Protocol ID
2) SAE information:
   - SAE name
   - Initial/Follow-up
   - Internal SAE code assigned by the Sponsor (this field is filled out by the Sponsor)
3) Information on the investigator who reported the SAE, and information on the study site:
   - Full name of the investigator who reported the SAE

- Contact information (tel. and e-mail)
- Site name and code
- Principal Investigator's name

4) Information on the study subject:

Patient ID

- Sex
- Body weight
- Height
- Date of birth
- Renal/hepatic impairment
- Pregnancy
- Allergies

5) Information on the test drug:

- INN and trade name (if this is a blind study, names are listed with “/")
- Indication
- Date of the first dose
- Number of therapy cycles received (if applicable)
- Drug batch (after which the SAE developed)
- Dose (with which the SAE occurred)
- Treatment start date and time (followed by the SAE)
- Treatment stop date and time (followed by the SAE)
- Route of administration
- Dosage and dosing frequency
- Is the therapy code disclosed or not (for blind studies)

6) Information about recent (within one month) concomitant therapy or that used at the time of SAE onset;

- INNs and brand names of concomitant medications
- Indication
- Treatment start date
- Treatment stop date
- Dosages, frequency, and route of administration
- Any suspected causal relationship between the SAE and concomitant medications

7) SAE narrative:

- SAE description with all symptoms and laboratory/instrumental abnormalities and periods indicated.
- Time after the last dose of the investigational product
- Autopsy data if the subject died (specifying the cause of death according to postmortem conclusion). If no autopsy findings are available, the cause of death should be specified according to the clinical conclusion.
- Time of hospitalization (if applicable)

8) Severity (CTCAE 4.03)

9) Seriousness

10) Medical history (with dates)

11) Investigations of particular interest at onset of the SAE

- Investigation
- Normal limits
- Date of the analysis
- Result

12) Actions taken to resolve the SAE

- Medication / non-medication

  For medication therapy, the following should be specified: INNs and brand names of drugs, treatment start and stop dates, dosages, frequencies, and routes of administration.

13) Actions taken regarding the investigational product

- Discontinued/ dose reduce / unchanged
- Dechallenge/rechallenge test results (if applicable)

14) Outcome

15) Signatures

The investigator **must** sign (with a signature and full name) each page of the SAE Report Form to verify his/her responsibility for the reported information. Signed SAE Report Form is then submitted to the Sponsor.

8.4. Methods and duration of follow-up of study subjects who had an AE/SAE

If the patient discontinues the study due to an AE/SAE, the investigator will conduct further treatment and follow-up in accordance with the in-house standard of care for this particular AE/SAE. The patient should be followed up until **the AE/SAE resolves completely**. In case of

any laboratory, instrumental or vital sign abnormality, the patient should be followed up until the events is completely resolved (or until the value is back to the baseline level).

See section 5.4 for further details.

The patient withdrawn from the study due to pregnancy that occurred during the study should be monitored through the entire pregnancy and for 6 months after delivery to evaluate the mother's and child's health. Information on pregnancy course and outcome should be recorded in the source documentation. During the entire period of pregnancy, the investigator in collaboration with the attending Ob/Gyn specialist should monitor the patient's overall health, the course of pregnancy, and laboratory values including ultrasound. When the child is born, the investigator together with the attending pediatrician should monitor the newborn for 6 months evaluating the child's clinical status and the laboratory/instrumental findings.

If the study subject's partner becomes pregnant, the study subject should provide the contacts of attending Ob/Gyn specialist to the Investigator. The investigator should monitor woman's health over the entire course of pregnancy. The investigator should monitor the pregnancy course via phone calls to attending Ob/Gyn specialist once every 3 months to assess the overall woman's health, pregnancy course, and laboratory/instrumental findings including the ultrasound. When the child is born, the investigator together with the attending pediatrician should monitor the newborn for 6 months evaluating the child's clinical status and the laboratory/instrumental findings.

9. STATISTICS

9.1. Description of statistical methods

The statistical analysis will be performed using two-tailed hypothesis tests. The statistical significance level is 0.05.

The Shapiro-Wilk test will be used to test the qualitative data for normality.

The normally distributed quantitative data will be analyzed using the dependent-sample *t*-test and ANOVA. The non-normally distributed data will be analyzed using the Mann-Whitney test and ANOVA. The regression analysis will be used for the quantitative efficacy data. The categorical data will be processed using the Fisher's exact test, Yates-corrected χ^2 test, and Cochran-Mantel-Haenszel test.

To describe the quantitative variables with normal distribution, the following parameters are used: means, SDs, min, max, and coefficient of variation. Non-normally distributed quantitative data will be described as medians and quartiles, min, max, and coefficient of variance.

The hypothesis of BCD-085 being superior to placebo will be tested by comparing the arms by the 95% CIs for the primary endpoint.

Statistical methods will be chosen based on the type and distribution of raw data. Appropriate statistical methods will be determined after the completion of data collection since data distribution and sample homogeneity cannot be assessed in advance. A list of methods may be expanded if necessary for conducting a high-quality study.

[redacted]

[redacted]

9.2. Statistical analysis steps and timelines for reports

The final report will contain results of the [redacted] safety, and efficacy endpoint analysis after the 14-week observation for 120 patients.

9.3. Planned number of subjects. Justification of sample size, including reasoning or calculations to justify statistical power and clinical justification of the study

This study is to test the hypothesis of the test drug being superior to placebo (H_0:$\varepsilon \leq \delta$, H_1:$\varepsilon > \delta$, where ε is the true difference in the mean efficacy level between the arms, δ is the margin of clinically non-meaningful differences between the test arm and the placebo arm). The error levels were set as follows: Type 1 error of 5% (α=0.05); type 2 error of 20% (β=0.2); power of 80%.

The sample size required to run the study was calculated on the basis of the literature data on clinical efficacy of drugs inhibiting IL-17 signaling.

The efficacy criterion used to calculate the sample size was the proportion of patients with moderate to severe plaque psoriasis who achieved a PASI75 at Week 12 of ixekizumab therapy in a clinical study that had the same design as the planned study[67]. The proportion of PASI75 [redacted]

1. The efficacy in the test arm (p_T) and in the placebo arm (p_{pl}): [redacted]
2. The true difference in the frequencies between the test and the placebo arms: [redacted]
3. z_α and z_β – quantiles of normal distribution N(0,1) (mean: 0, standard deviation: 1).
4. k- the ratio between the sample sizes between the arms (placebo-to-test) :
   $n_{pl}/n_T = k$.
5. The superiority margin was set as follows: [redacted]

[67]Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012 Mar 29;366(13):1190-9.

With the method described by [Chow Sh.-Ch., Shao J., Wang H, 2008], the sample size was calculated assuming that the size of the test sample (n_T) is the same as the size of the placebo sample (n_{pl}), i.e.. k = 1.

$$n_T = n_{pl} = \frac{(z_\alpha + z_\beta)^2 * \left(\frac{p_T*(1-p_T)}{k} + p_{pl} * (1 - p_{pl})\right)}{(\varepsilon - \delta)^2} =$$

[redacted]

Thus, the study aimed at proving the efficacy of BCD-085 has to involve at least 20 patients (5 in each of 4 arms). However, such small samples do not allow reliably evaluating the drug safety [redacted] and performing appropriate inter-group comparisons. Moreover, an account should be made for potential dropouts due to reasons not related to the study therapy.

With this being said, the final number of subjects was set as 30 per arm (the overall sample size is 120 patients). This sample size allows evaluating adverse events that occur in more than 1 of 10 patients, ensures the significance [redacted] data collected in the study, and allows comparing the effects seen with different doses of BCD-085.

[redacted]

9.4. Suitable significance level

The level of significance was set as 0.05 (5%) with the statistical power of 0.8 (80%).

9.5. Statistical criteria for study stopping/terminating the study

Not specified by the Protocol.

9.6. Handling of missing, unevaluable or uncertain data

All information specified in the eCRF should be confirmed by corresponding data in source documents.

[68] Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D, Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012 Mar 29;366(13):1190-9.

Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. Br J Dermatol 2013;168(2):412-21.

After entering all data in the electronic database, an employee keeping the database checks it for inconsistencies, errors, and missing data points. To collect missing data or correct wrong data, the BIOCAD's Medical Expert generates queries, which are study- and site-specific, i.e. generated for each subject individually. The Clinical Study Monitor will send queries to the study center by fax or e-mail. The investigator must respond within 5 working days from the date when the query was received. Copies of responses to queries must be kept at the study site; original responses must be stored at JSC BIOCAD.

When responses to queries are received from investigators, the employee keeping the database checks it for inconsistencies, errors, and missing data points. When all the data from all the centers are collected and entered, the database is locked, and the statistical processing can be performed.

Missing, not evaluable or uncertain data will not be replaced.

Uncertain or unevaluable data will be detected during the outlier analysis by examination of Mahalanobis or Cook distance, visual analysis of scattering diagrams and box-plots. Data suspected to be outliers will be processed by the biomedical statistician together with the medical expert and, if necessary, the principal investigator.

9.7. Reporting any deviations from the initial statistical plan

If the initial study plan requires modifications, all changes will be described and explained in a protocol amendment or interim/final clinical study report.

If initially defined statistical methods cannot be used, the changes should be presented in the final statistical report and the clinical study report. Justification of these changes should be given with the references to calculations, statistical parameters, and analysis of a situation that led to these changes. Decisions regarding emergency deviations (data-modifying allowances) can be made only by the Sponsor. These decisions must be explained and justified, including in the final study report.

9.8. Selection of subjects for analysis

Safety analysis

The safety analysis will include all patients who received at least one dose of the investigational product. Additionally, the SAE analysis will include all randomized patients starting from the ICF signing and until the end of their participation in the study.

Efficacy analysis

Per protocol, the efficacy analysis is to include all patients who received at least one dose of BCD-085/placebo and who attended at least one visit next visit. If no data are available at Week 12, the data from the last assessment are to be used (last-observation-carried-forward method). In addition, these patients should be considered non-responders and analyzed separately.

[redacted]

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution involved in the study must ensure direct access to source data/documents by the monitor, the auditor, the LEC/IRB or regulatory authorities.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data quality assurance

According to ICH GCP and regulatory requirements, the Sponsor, the third party on its behalf, regulatory authorities, or local ethics committees can perform audits (inspections) to assure quality any time during the study or after its completion. The investigator is responsible for providing medical auditors the access to all study documentation including the source documentation, and for allowing his/her time and time of the study team to discuss the audit/inspection results and other matters with the medical auditor.

11.2. Protocol compliance by investigator

Before beginning the study, the investigator must read and accept all provisions of this Protocol. The investigator must conduct the study in accordance with this Protocol, the ICH GCP, and other regulatory requirements of participating countries.

No protocol deviations are allowed during the study without a previous written approval of JSC BIOCAD, the Ministry of Healthcare of the Russian Federation and Local Ethics Committees, except for the cases when it was necessary to protect a patient from an immediate hazard.

The investigator should have enough time to accurately perform and complete the study within the time limits specified by JSC BIOCAD, enough employees of appropriate qualification, and adequate equipment to conduct the study according to the Protocol.

Each sub-investigator participating in the study must read the Protocol and be aware of his/her responsibilities/functions in the study. If the principal investigator delegates some of his/her functions to sub-investigators, this must be documented in a relevant section of the Investigator's File.

11.3. Investigator's responsibility to comply with the Protocol

At each study site, the decision regarding patient's early withdrawal from the study has to be approved by JSC BIOCAD.

If the investigator decides to withdraw a patient from the study, he/she must send a request (specifying a reason for withdrawal) to BIOCAD's Medical Advisory Division by fax: [redacted] Within 48 hours (except for weekends and public holidays) from the time when the request was received by the Medical Advisory Department, JSC BIOCAD should notify the investigator of the decision regarding patient withdrawal. If a patient has to be immediately withdrawn from the study due to an SAE, the investigator must inform JSC BIOCAD about the SAE within 24 hours but does not have to wait for approval from JSC BIOCAD.

If a patient does not attend a scheduled visit or makes unauthorized changes in the dose of the investigational product, the investigator must report the violation to the Medical Advisory Division of JSC BIOCAD within 24 hours from the time of awareness (by fax [redacted] Medical advisors will instruct the investigator on further case management and on how to document the causes of the violations in the CRF/source documents.

If the investigator fails to follow these procedures or if multiple Protocol violations occur, JSC BIOCAD may suspend or terminate the study at this particular study site.

11.4. Study monitoring

Before the study beginning (at the Study Initiation Visit or investigators' meeting), a representative (CRA) of JSC BIOCAD (or an authorized CRO) will explain the Protocol and CRF to the investigators and members of the study teams. During the study, the CRA will regularly visit the study center to check the completeness of subjects' documentation, the accuracy of information in the CRF, the conformance to the Protocol and GCP, patients' recruitment, and storage, dispensing, and accounting of the investigational products according to the requirements. During these visits, key members of the study team should be available to assist the CRA and resolve arising issues (if any).

Study monitoring is performed according to appropriate SOPs of JSC BIOCAD.

For each study subject, the investigator should keep source documents containing data about the subject and records made during visits (medical records of the study center), including demographics, medical information, laboratory findings, ECG, and all other tests or examinations. Any information in the CRF should be also recorded in the patient's source documents. The investigator must keep the original ICF. A copy of the signed ICF will be given to the patient.

The investigator should provide the CRA with all relevant source documents of the patient to confirm that data in them correspond to those in the CRF. The investigator should ensure the timely completeness of the CRFs before the CRA's visit.

The CRA will check the CRFs and other study materials comparing them against the source data to confirm that the study complies with the Declaration of Helsinki, the ICH GCP, regulatory requirements of participating countries, and the Study Protocol, and to confirm the authenticity, accuracy, and completeness of data.

Upon the completion of the study, a representative of JSC BIOCAD (CRA) should visit the study center to perform the end-of-study visit. During this visit, the Sponsor's representative will collect all necessary documentation in accordance with the SOP of JSC BIOCAD.

11.5. Data management and quality control

In the trials with eCRFs, JSC BIOCAD employees (or employees of an authorized CRO) will check the data entered by the study team members for accuracy and completeness. If there are any inconsistent or missing data points, queries are generated with a request for clarification. All queries are sent to the study site. A designated member of the study team must immediately answer the request and make all required changes to the database.

At the end of the study, any protocol deviations will be determined. After clarifying protocol deviations and confirming the completeness and accuracy of the data, the database is locked, the blind codes are opened, and the data are ready for analysis.

11.6. Study termination

JSC BIOCAD can suspend or terminate the study due to safety or ethical issues, Protocol compliance issues, or other reasons. If JSC BIOCAD suspends or terminates the study, the study site will be notified in advance. In case of suspension or termination, JSC BIOCAD and the investigator have to inform Ethics Committee and regulatory authorities in due time. If the study is suspended or terminated, all study information must be transferred to and all unused investigational product must be returned to JSC BIOCAD.

12. ETHICS

12.1. Ethical aspects of the study

The study will be conducted in accordance with the ethical principles stated in the World Medical Association Declaration of Helsinki (Recommendations guiding physicians in biomedical research involving human subjects, 1964-1996) and the ICH GCP principles.

Before the study start, the final version of the Protocol including Patient Information Sheet and Informed Consent Form will be submitted for approval to the Ministry of Healthcare of the Russian Federation, to Local Ethics Committees, and to regulatory authorities of participating countries.

All subsequent protocol amendments (other than administrative amendments) must be approved before implementation.

Informed consent must be obtained from patients before starting any study procedures. The Patient Information Sheet contains all the information that a patient may need to make a conscious and independent decision about whether to participate.

During the study, all cases of SAEs will be reported to JSC BIOCAD within 24 hours. JSC BIOCAD will analyze the reports and may suspend the study if considered necessary. Local ethics committees will also be notified of all SAEs that are related, in investigator’s opinion, to the investigational product.

All patient personal information is confidential and can be disclosed only if required by law (including court decisions).

All study subjects will be insured. If a patient is injured directly due to the investigational product, the Sponsor will cover all reasonably justified treatment expenses.

12.2. Confidentiality of study subjects

The investigator shall protect the confidentiality of the trial subjects, the text of this Protocol, and all other study materials and results.

The investigator must ensure patient anonymity. In the CRFs and other documents provided by JSC BIOCAD, patients should be identified by ID codes and/or initials, but never by their names.

The investigator should keep a separate log with patients' IDs, last names, addresses, phone numbers, and medical record numbers (if applicable). The investigator must keep data not intended for submission to JSC BIOCAD strictly confidential.

No study materials proprietary to JSC BIOCAD can be transferred to a third party unless required by the law of the Russian Federation.

13. DATA HANDLING AND RECORD KEEPING

13.1. Record keeping at the study site

All study documents must be archived at the study site or at the central archive of the institution. A list of all study subject identifiers should be made.

According to the ICH GCP, essential documents include: signed protocol and amendments; copies of completed CRFs; signed ICFs for all patients; medical records; diaries and other source documents; approvals from IECs/regulatory authorities and all correspondence including approved documents; drug accountability records; study correspondence; and the list of patient names and addresses. These essential documents must be kept in the Investigator’s File.

The investigator must retain copies of all essential documents for 5 years.

By the end of this period, the Sponsor will inform the investigator(s) about the date when the documents may be destroyed.

Study subject documentation will be archived in accordance with the site in-house SOPs.

The investigator must inform the Sponsor about the place where essential documents are stored and request an approval from JSC BIOCAD before destroying any of essential documents. Appropriate measures must be taken to prevent the accidental or premature destruction of these documents.

13.2. Confidentiality of data

All information about study subjects will be kept confidential. The information will be processed in compliance with all applicable laws and regulations. These regulations require that the patients be informed and give their written consent about the following questions:

- What protected health information will be collected in this study?
- Who will have access to this information and on what grounds?
- Who will use or disclose this information?
- Do study subjects have the right to recall their consent for using their confidential health information?

According to the current regulations, in case the patient recalls his/her authorization to collect or use his/her protected health information, the investigator still can use all information obtained before the authorization was withdrawn. In patients who withdrew their consent for collection or use of confidential health data, all efforts should be made to obtain a consent at least for collecting information for safety follow-up (i.e. development or deterioration of existing adverse events) at the end of the scheduled participation in the study.

To prevent the confidential subjects' information from unauthorized access, the study data collection system has safety elements for encryption of all data to be sent in both directions. The access to the system will be controlled via individually assigned ID codes and user passwords issued only to the authorized and adequately trained personnel. They will be given only to authorized members of the study team who have undergone a special training.

[redacted]

13.3. Collection of data

This trial uses an electronic data capture (EDC) system. Designated study team members will enter the data required by the Protocol to eCRFs. The eCRFs have been developed with a

validated and safe web-based software. The study team members will get access to the EDC system only after being appropriately trained. An automated validation program inspects eCRFs for inconsistencies and allows the study team members to change or verify the entered data.

The principal investigator is responsible for completeness and accuracy of all the data entered to the eCRFs and for entering and updating the information in a timely manner.

Members of the study team will collect blood samples for the assessments of [redacted] safety of BCD-085. The samples will be then sent to the central laboratory for processing.

X-ray or fluorography scans of the chest will be obtained at the study sites and interpreted locally. The study team member can send the scans to an appropriate institution assigned by JSC BIOCAD for centralized review and quality control.

[redacted]

14. REIMBURSEMENT AND INSURANCE

[redacted]

The compensation [redacted] The Sponsor will not reimburse the patient's expenses for getting to the study center or other additional charges. The compensation is subject to taxation according to the local law.

[redacted]

During the study, each study subject will be insured as a study participant according to the applicable law of the participating country. In the Russian Federation, patients will be insured by [redacted]

The investigator will give a copy of the Compulsory Insurance Agreement to the patient and explain its terms and conditions (including the responsibilities of patients participating in the study). The investigator will also give the patient a certificate of compulsory insurance of the life and health of a drug clinical study participant. If the patient needs to make changes to the compulsory insurance certificate, the patient will need to return the previously issued certificate and receive a new one (issued within 2 working days).

The insurance covers claims from study participants to the Insurer exclusively concerning reimbursement of inflicted damage to the life and health that occurred while the subject was participating in the clinical study. This inflicted damage is to be due to disadvantages of investigational products or insufficient information on them, unintended errors or neglect. Only claims first asserted to the Insurer within the insurance period concerning events that took place in the insurance territory from the beginning of the study and associated with the insured activity (the study) are covered.

If the patient is injured due to the study drug or a medical procedure as per the Study Protocol, the patient will receive sufficient qualified medical care for free (paid by the Insurance company). The Insurance Company will pay for the research-related injury provided the patient adheres to all instructions of the investigator.

The Insurer shall pay the following compensation amounts according to the compulsory Insurance Agreement (insurance payment):

[redacted]

Patients in other participating countries will be insured throughout the entire study according to the law of the participating country.

15. PUBLICATIONS

After completion of the study, its results will be summarized and prepared for publication. The investigator must not publish any study results, including those obtained in his/her study site,

without a permission from JSC BIOCAD. Results from individual study sites must not be published before the publication of the overall study results.

16. APPENDICES

Appendix 1. SF-36 (Short Form Health Survey)

SF-36 questionnaire

Instructions: Note: This survey contains questions to find out how do you feel about your health. This information will help us to monitor your health and how easily you perform your usual activities. Please answer each question by marking your response as shown below. If you are not sure how to answer, please choose one option that reflects your opinion the best. Please encircle only one digit in each line.

In general, would you say your health as:

Excellent	Very good	Good	Fair	Poor
1	2	3	4	5

Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same	Somewhat worse now than one year ago	Much worse now than one year ago
1	2	3	4	5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c: Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3

g. Walking more than a mile	1	2	3
h. Walking several blocks	1	2	3
i. Walking one block	1	2	3
j. Bathing or dressing yourself	1	2	3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	**Yes or**	**No**
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c: Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	**Yes or**	**No**
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c: Didn't do work or other activities as carefully as usual	1	2

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Strongly	Extremely
1	2	3	4	5

How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
1	2	3	4	5	6

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Please give one answer.

Not at all	Slightly	Moderately	Strongly	Extremely
1	2	3	4	5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c: Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

During the past 4 weeks, how much of the time has <u>your physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)? Please give one answer.

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

How TRUE or FALSE is <u>each</u> of the following:	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
A. I seem to get sick a little easier than other people	1	2	3	4	5

B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

Appendix 2. Form for registration of injection site reactions.

FORM FOR REGISTRATION OF INJECTION SITE REACTIONS

Visit No: __ __
Product: BCD-085/placebo
Injection No. **Date of the injection** / /201

Brief description:

Severity* **1□ 2□ 3□ 4□**

First signs developed _____ after injection

Clinically meaningful? Yes / No Does it meet the SAE criteria?** Yes / No

Appearance	**Revealed**	**Size cm**	**Onset date**	**End date**
Hyperemia	Yes / No		___/___/201__	___/___/201__
Edema	Yes / No		___/___/201__	___/___/201__
Blister	Yes / No		___/___/201__	___/___/201__
Infiltrate	Yes / No		___/___/201__	___/___/201__
Necrosis	Yes / No		___/___/201__	___/___/201__
Ulcer	Yes / No		___/___/201__	___/___/201__
Cyanosis/bruise	Yes / No		___/___/201__	___/___/201__
Pain	Yes / No	Score____***	___/___/201__	___/___/201__
Other: _____	Yes / No		___/___/201__	___/___/201__

Had a consultation with a surgeon/dermatologist Yes/No

Results of consultation:

Performed medication and non-medication treatment, outcome:

*** classification of severity grades of local reactions**
1. Mild: transient symptoms or mild discomfort lasting for less than 2 days and not requiring treatment or another intervention.
2. Moderate: mild or moderate limitation of everyday activity; assistance may be required; medication therapy is minimum or not required.
3. Severe: significant limitation of everyday activity; assistance is required; medication therapy is required; hospitalization may be required.
4. Life-threatening: severe limitation of everyday activity; significant assistance is required; medication therapy is required; hospitalization is required.

****in case of an SAE, fill out the SAE Report Form in the CRF**

*** The assessment of pain by the study subject with the visual scale (in scores). Where 0 – there is no pain; 10 – the most severe, insupportable, intolerable pain in the opinion of the subject.