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CLINICAL STUDY PROTOCOL

Protocol title:	An International, Multicenter, Randomized, Double-blind, Placebo-Controlled Clinical Study to Compare the Efficacy and Safety of Two Dosing Regimens of BCD-085 (JSC BIOCAD, Russia) in Patients with Moderate to Severe Plaque Psoriasis
Protocol ID:	BCD-085-7
Protocol date:	October 02, 2017
Protocol Amendment:	1
Protocol Amendment date:	November 02, 2018
Protocol version:	2.0
Study Sponsor/Clinical Research Associate:	JSC BIOCAD, Russia Legal address: 34A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, 198515 Mailing address: Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 [redacted]
Name and job title of persons authorized to sign the Protocol and Protocol amendments on behalf of the Sponsor:	[redacted] Address: Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 [redacted]
Name, job title, address and telephone of Medical Expert appointed by the Sponsor for this study:	[redacted] 34A, Ul. Svyazi, Strelna, Petrodvortsoviy District, Russian Federation, 198515 e-mail: [redacted]

The information presented in this document is confidential and intended to be used solely by investigators, ethics committee members, and health care authorities. The information contained in this protocol should 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.
The above-mentioned requirements become effective upon the signing of this Protocol.

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SIGNATURE SHEET

To Protocol version 2.0 of November 02, 2018: "An International, Multicenter, Randomized, Double-blind, Placebo-Controlled Clinical Study to Compare the Efficacy and Safety of Two Dosing Regimens of BCD-085 (JSC BIOCAD, Russia) 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 study as outlined in this Protocol, the ICH GCP, and applicable regulations 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]

_____
Signature

_____
Date

ABBREVIATIONS

AUC	Area under the concentration vs. time curve
AE	Adverse event
ALT	Alanine transaminase
AnSc	Anaphylaxis score
AP	Alkaline phosphatase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUMC	Area under the first moment curve
BAbs	Binding antibodies
BCD-085	Monoclonal anti-IL17 antibody manufactured by JSC BIOCAD
BP	Blood pressure
BSA	Body surface area affected
CHF	Congestive heart failure
Cl	Total clearance
C_{max}	Maximum drug concentration in the plasma
C_{min}	Minimum concentration
CNS	Central nervous system
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DLQI	Dermatology Quality of Life Index
DNA	Deoxyribonucleic acid
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HBcor	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoproteins
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
INN	International non-proprietary name
ITT	Intention-to-treat population (all patients who were randomized in the study, whether they completed the study per protocol or discontinued it due to any reason)
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
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-protocol population (all patients who completed the study per protocol)
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RNA	Ribonucleic acid

SAE	Serious adverse event
SOP	Standard Operating Procedure
sPGA	Static Physician's Global Assessment
SS	Separate subdivision
t½	Elimination half-life
TC	Total cholesterol
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. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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 drug product being tested in the clinical study.
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)	Case report form is a printed or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.
Investigator's Brochure	Investigator's Brochure is 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 |__|__|-|__|__|__|	A unique identifier assigned by the Investigator to each study subject to protect the subject's identity and used instead of the subject's name when the Investigator reports adverse events and/or other study-related data. Usually, this number consists of a two-digit study site number and a three-digit sequential number (showing the order how the patients were included in the study).
Screening number |__|__|-|__|__|__|	A unique number assigned to each patient who signed an informed consent form. It consists of a two-digit study site number and a three-digit sequential number, which shows the order how patients were enrolled in this center.
Randomization number	A unique number assigned to each patient included to the study (randomized) and coding a specified therapy. After randomization, this number is not used anywhere.
Assessment	A procedure used to obtain data required in the study.
Inclusion in the study	Time point corresponding to randomization and assigning to therapy groups.

Term	Definition
Any other therapy during 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.
Patient's premature withdrawal (dropout)	The time point when the patient discontinues the study before the planned completion of the study therapy and/or assessments. At this time point, the study therapy stops, and no further assessments are planned (follow-up for survival and/or disease progression may be an exception). 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.
Completion of the study	The time point corresponding to the final patient's 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.
Discontinuation of study therapy	Time point when the investigational therapy is terminated regardless of what caused the termination. It does not necessarily coincide with patient's withdrawal from the study.
Variable	An identifier used in data analysis; it is obtained directly or indirectly from data gained during the specified assessment within the specified time points.

DOCUMENT HISTORY

Document	Version date	Narrative of changes
Version 1.0	October 02, 2017	N/A
Version 2.0 (with Amendment 1)	November 02, 2018	Extension of treatment with BCD-085 to 154 weeks (extension of the study for Arms 1 and 2 to 158 weeks and for Arm 3 to 170 weeks). Clarifications and amendments in the text. Editorial corrections. Results obtained in extension periods of the studies evaluating the efficacy and safety of BCD-085 in patients with psoriasis and ankylosing spondylitis were introduced (BCD-085-2ext and BCD-085-3ext). Supersedes: Protocol Version 1.0 of October 02, 2017.

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

#	Name and job title of Principal Investigator	Name of study (clinical) site	Address, telephone, fax and e-mail of study (clinical) site
		Study sites in the Russian Federation	
1.	[redacted]	Federal State Budgetary Educational Institution of Higher Education V.I. Razumovsky Saratov State Medical University of the Ministry of Healthcare of the Russian Federation, study site located at Skin and STD Clinic	[redacted]
2.	[redacted]	Federal State Institution Siberian District Medical Center of the Federal Medical and Biological Agency	[redacted]

	[redacted]		[redacted]
3.	[redacted]	State Budgetary Educational Institution of Higher Professional Education Tver State Medical Academy of the Ministry of Healthcare of the Russian Federation, study site located at Limited Liability Company Professor's Clinic	
4.	[redacted]	Regional State Budgetary Healthcare Institution Smolensk Dermatology and Venereology Clinic	
5.	[redacted]	Limited Liability Company Occupational Health Facility 157	

6.	[redacted]	Limited Liability Company MedPomosch	[redacted]
7.	[redacted]	State Budgetary Healthcare Institution Chelyabinsk Regional Clinical Skin and STD Clinic	
8.	[redacted]	Federal State Budgetary Scientific Institution V.A. Nasonova Research Institute of Rheumatology	
9.	[redacted]	Federal 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	
10.	[redacted]	State Budgetary Institution of Sverdlovsk Region Ural Research Institute Dermatology, Venereology and Immunopathology	

11.	[redacted]	Federal State Budgetary Institution State Scientific Center of Dermatology, Venereology and Esthetic Medicine of Ministry of Healthcare of the Russian Federation	[redacted]
12.	[redacted]	Limited Liability Company Sanavita	
13.	[redacted]	State Autonomous Healthcare Institution Republican Clinical Dermatology and Venereology Clinic	
14.	[redacted]	Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow Medical University of Ministry of Healthcare of the Russian Federation (Sechenov University), study site located at Skin and STD Clinic	

15.	[redacted]	Federal State Autonomous Educational Institution of Higher Education V.I. Vernadskiy Crimea Federal University	[redacted]
16.	[redacted]	Federal State Budgetary Educational Institution of Higher Education I.I. Mechnikov North-Western State Medical University of the Ministry of Healthcare of the Russian Federation, study site located at P.N. Kashkin Medical Mycology Scientific Research Institute	
17.	[redacted]	Federal State Budgetary Military Educational Institution of Higher Education S.M. Kirov Military Medical Academy of the Ministry of Defense of the Russian Federation	
18.	[redacted]	Limited Liability Company Pierre Wolkenstein Skin Diseases Clinic	

19.		Federal State Budgetary Educational Institution of Higher Education Academician I.P. Pavlov First St. Petersburg State Medical University of Ministry of Healthcare of the Russian Federation	
20.		Ryazan Region State Budgetary Institution Regional Clinical Dermatology and Venereology Dispensary	
21.		State Healthcare Institution Regional Dermatology and Venereology Clinic	
22.		Limited Liability Company Medical Center Azbuka Zdorovya	
23.		Federal State Budgetary Educational Institution of Higher Education Siberian State Medical University of	

	[redacted]	Ministry of Healthcare of the Russian Federation	[redacted]
24.	[redacted]	Limited Liability Company Technology of Health	
25.	[redacted]	State Budgetary Healthcare Institution Clinical Dermatology and Venereology Clinic of Ministry of Healthcare of Krasnodar Region	
26.	[redacted]	State Budgetary Clinical Healthcare Institution of Yaroslavl Region N.A. Semashko Municipal Hospital, study site located at Therapy Department	
27.	[redacted]	State Budgetary Moscow Healthcare Institution Moscow Research and Practice Center of Dermatovenereology and Cosmetology of Moscow Healthcare Department	

			[redacted]
Study sites in the Republic of Belarus			
1.	[redacted]	Healthcare Institution Vitebsk Regional Clinical Center of Dermatology, Venereology and Esthetic Medicine	[redacted]
2.	[redacted]	Healthcare Institution Mogilev Regional Dermatology and Venereology Dispensary	
3.	[redacted]	Healthcare Institution Municipal Clinical Skin and STD Clinic	
4.	[redacted]	Institution Gomel Regional Clinical Skin and STD Clinic	

SYNOPSIS	
Protocol ID	BCD-085-7
Study title	An International, Multicenter, Randomized, Double-blind, Placebo-Controlled Clinical Study to Compare the Efficacy and Safety of Two Dosing Regimens of BCD-085 (JSC BIOCAD, Russia) in Patients with Moderate to Severe Plaque Psoriasis
Phase	III
Study Sponsor	JSC BIOCAD Mailing address: Petrovo-Dalnee, Krasnogorskiy District, Moscow Region, Russian Federation, 143422. Legal address: 34A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russian Federation, 198515.
Test drug	BCD-085 [redacted]
Placebo	[redacted]
Study aims and objectives	**Study aims:** To evaluate the efficacy and safety of BCD-085 once every 4 weeks vs. BCD-085 once every 2 weeks (standard dosing regimen) vs. placebo. **Objectives of the main study period** 1. To compare the efficacy of BCD-085 in two dosing regimens and placebo using PASI 75 rate, sPGA score, and other secondary efficacy measures after 12 weeks of the treatment. 2. To compare the efficacy of BCD-085 in two dosing regimens and placebo using PASI 75 rate, sPGA score, and other secondary efficacy measures after 52 weeks of the treatment. 3. To evaluate the proportion of patients in each study arm who developed adverse events with repeated administration of BCD-085 or placebo. To compare the safety profiles of BCD-085 Q4W and BCD-085 Q2W.

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	4. To assess the immunogenicity of BCD-085 defined as the proportion of patients who developed anti-drug antibodies (binding/neutralizing). **Objectives of the extension study period** 1. To assess maintenance of response during the long-term treatment with BCD-085 (for up to 154 weeks) and evaluate the safety profile of such treatment. 2. To assess the immunogenicity of BCD-085 defined as the proportion of patients who developed anti-drug antibodies (binding/neutralizing).
Study design	The BCD-085-7 study is an international multicenter, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of two dosing regimens of BCD-085 (JSC BIOCAD, Russia) in patients with moderate to severe plaque psoriasis (Phase III). The study is planned to enroll 213 adult patients with moderate to severe plaque psoriasis (diagnosed at least 6 months before signing the informed consent form) who have BSA ≥ 10%, PASI score ≥ 10[1], and sPGA score ≥ 3. Before being screened for the study, patients must read and sign the informed consent form and undergo a screening examination (within 28 calendar days) to confirm that they are eligible for the study. The Protocol does not provide any additional requirements regarding the diet or physical activity during the screening or study period. **Stratification and randomization** When the Investigator has decided that the patient can take part in the study, the patient should be stratified according to his/her body weight (<100 kg/≥100 kg), previous use of monoclonal antibodies for the treatment of psoriasis (previously treated/naive), PASI score (<20/≥20), and psoriatic arthritis (yes/no) and randomized at a 2:2:1 ratio to one of the three study groups: 1) BCD-085 Q2W (Arm 1), 2) BCD-085 Q4W (Arm 2), 3) placebo (Arm 3).

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

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	Study periods 1. Screening (up to 28 days from signing the Patient Information Sheet with the Informed Consent Form, inclusive); 2. Main treatment period (from Week 0 through Week 54) 3. Extension study period 1) For Arms 1 and 2: from Week 54 through Week 154 2) For Arm 3: from Week 54 through Week 166 4. Follow-up period 1) For Arms 1 and 2: from Week 154 through Week 158 2) For Arm 3: from Week 166 through Week 170 **Screening period:** Up to 28 days from signing the Patient Information Sheet with the Informed Consent Form, inclusive. **Main treatment period (Week 0 through Week 54):** In this study period patients will be distributed to three arms: • **Arm 1:** Patients in this arm (85 subjects) will receive BCD-085 120 mg (two subcutaneous injections, 60 mg in 1.0 mL each) once a week during the first 3 weeks (induction) and then once every 2 weeks through Week 10. Thus, the investigational product will be administered on Day 1 of Week 0, Week 1, Week 2, Week 4, Week 6, Week 8, and Week 10. • **Arm 2:** Patients in this arm (85 subjects) will receive BCD-085 120 mg (two subcutaneous injections, 60 mg in 1.0 mL each) once a week during the first 3 weeks (induction) and then once every 4 weeks through Week 10. Thus, the investigational product will be administered on Day 1 of Week 0, Week 1, Week 2, Week 6 and Week 10. To maintain the study blind, patients of this arm will receive placebo (2 injections) on Day 1 of Week 4 and Week 8. • **Arm 3:** Patients of this arm (43 subjects) will receive placebo (2 subcutaneous injections of placebo, 1.0 mL each) on Day 1 of Week 0, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10.

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	On Week 12, the treatment efficacy will be assessed with a PASI 75 score, and the treatment will be **unblinded**. Patients from Arms 1 and 2 will be given BCD-085 once every 4 weeks. Patients from Arm 3 will receive BCD-085 as follows: ✓ Induction: Weeks 12, 13, and 14, once a week; ✓ Weeks 18 through 50: once every 4 weeks. Therefore, there will be 3 arms even after unblinding, and patients will receive BCD-085 according to the regimens described below: a) Patients in Arm 1 will receive BCD-085 120 mg (2 SC injections of 60 mg each) once every 4 weeks starting from Week 14 through Week 50. b) Patients in Arm 2 will receive BCD-085 120 mg (2 SC injections of 60 mg each) once every 4 weeks starting from Week 14 through Week 50. c) Patients in Arm 3 will receive BCD-085 120 mg once a week at Weeks 12, 13, 14, then once every 4 weeks (Weeks 18, 22, 26, 30, 34, 38, 42, 46, 50). **Extension study period (from Week 54 through Week 154 for Arms 1 and 2, through Week 166 for Arm 3):** During **the extension study period** all patients who achieved PASI 75 at Week 52 will receive BCD-085 120 mg once every 4 weeks: a) Patients from Arm 1 will receive BCD-085 from Week 54 through Week 154. b) Patients from Arm 2 will receive BCD-085 from Week 54 through Week 154. c) Patients from Arm 3 will receive BCD-085 from Week 54 through Week 166. Patients who failed to achieve PASI 75 at Week 52 will be withdrawn from the study.

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	In Arm 3, treatment will be extended by 12 weeks so that the total treatment duration in all arms can be 154 weeks. During the main treatment period (during the first 12 weeks of the study), patients from Arm 3 receive placebo, so the treatment period for these patients is extended to 166 weeks. Regardless of the arm where the patient is assigned to, during the main study period (Week 0 through Week 54) SC injections will be performed by an authorized member of the study team at the study site (except for the injection on Week 54). At Week 54 patients will be trained on how to self-inject the investigational product. If necessary, the training can be repeated at any of the subsequent visits. During the extension study period (Week 54 through Week 154 for patients from Arms 1 and 2, Week 54 to Week 166 for patients from Arm 3), patients will self-inject the investigational product at home after receiving relevant training at the study site. Injections of the investigational product on visit dates will be performed by an authorized member of the study team at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154 (in Arms 1 and 2) or at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154, 166 (in Arm 3). The first self-injection of the investigational product at Week 54 will be performed under the supervision of an authorized member of the study team. Patients from Arms 1 and 2 will self-inject the investigational product on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150, patients from Arm 3 – on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150, 158, 162. At each of visits from Week 54 to Week 146 (patients from Arms 1 and 2) and at each of visits from Week 54 to Week 154 (patients from Arm 3), BCD-085 will be dispensed to patients for self-administration at home at an amount sufficient until the next visit. **Follow-up period:**

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	Patients will be followed up for 4 weeks after the last injection (Week 154 to Week 158 for Arms 1 and 2, Week 166 to Week 170 for Arm 3).
Study population	Men and women aged from 18 years (inclusive) and older with a confirmed diagnosis of moderate to severe plaque psoriasis (lasting for at least 6 months before signing the ICF) who did not respond to/are candidates for systemic therapy including TNF-α inhibitors or UV therapy.
Planned sample size	213 patients.
Inclusion criteria	1. Signed informed consent form (ICF). 2. Age of at least 18 years old at the time of signing the ICF. 3. Moderate to severe plaque psoriasis diagnosed at least 6 months before signing the ICF. 4. Patients who received at least one course of phototherapy or [2] systemic therapy for psoriasis or are candidates[3] for such treatment according to the investigator. 5. Body surface area (BSA) affected by psoriasis of 10% or greater, the PASI score of 10 or greater, and the sPGA score of 3 or greater at screening. 6. 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). 7. The ability of the patient (in the Investigator's opinion) to follow the Protocol procedures. 8. Patients of both sexes and their partners with reproductive potential must implement reliable contraceptive methods starting from signing the ICF to 20 weeks after the last dose of the investigational product. This requirement does not apply to patients after surgical sterilization and to females who are post-menopausal for 2 years or longer. Reliable contraceptive methods include one barrier method in combination with one of

[2]Systemic therapy refers to any non-biologics (methotrexate, cyclosporine, acitretin, mycophenolate mofetil, apremilast, calcitriol derivatives, etc.), or genetically engineered biologics (TNF inhibitors, anticytokine drugs, anti-CD20 drugs, etc.).
[3]BCD-085 is planned to be used as either a first- or second-line treatment, so the study involves treatment-naive patients along with those who failed to respond to systemic therapy or phototherapy.

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	the following: spermicides, intrauterine device/oral contraceptives.
Exclusion criteria	1. Baseline erythrodermic, pustular, or guttate psoriasis or any other skin disorders (e.g. eczema) that can affect/complicate the assessment of psoriasis treatment. 2. Use of the following medications: • Prior exposure to any therapeutic monoclonal antibodies targeting IL-17 or its receptor; • Prior exposure to more than one drug containing monoclonal antibodies or their fragments; • Prior exposure to any monoclonal antibodies given within 12 weeks before signing the ICF; • Use of any systemic[4] medications for the treatment of psoriasis (including glucocorticoids, methotrexate, sulfasalazine, cyclosporine, acitretin, mycophenolate mofetil, apremilast, calcitriol derivatives, etc.) within 4 weeks before signing the ICF. If these drugs were stopped less than 4 weeks before signing the ICF, the screening period should be extended up to 8 weeks during which no new systemic drugs are allowed; • Use of phototherapy within 4 weeks before signing the ICF; • Use of topical[5] medications for the treatment of psoriasis within 2 weeks before signing the ICF; • Vaccination with live or attenuated vaccines within 8 weeks before signing the ICF. 3. Any active systemic infection or recurrent infection at screening/randomization. 4. HIV, hepatitis B, hepatitis C, or syphilis[6].

[4] Except for NSAIDs.

[5] Patients may use topical glucocorticoids (of mild to moderate potency) on the face, underarm, and genitals. Patients may also use topical moisturizers, emollients, oils, and salicylic acid ointments, topical antibacterial and/or antimycotic agents as needed. Patients should discontinue all local skin products (medications or cosmetics) 24 hours before the planned PASI assessment.

[6] The screening for HBV includes tests for HBsAg and total antibodies to HBcor antigen (anti-HBcor total = IgG + IgM). If the test results for these markers (HBsAg and anti-HBcor total) are negative, the patient is considered eligible for the study by this criterion. If the patient tests positive for HBsAg, the patient cannot be included in the study regardless of the results for anti-HBcor. If the test results for HBsAg are negative but anti-HBcor total antibodies are detected, the patient should undergo an additional examination. The additional examination should include the following: qualitative PCR for HBV DNA, anti-HBcor IgM, and a consultation with the Infectious Disease Specialist. The activity of liver transaminases and concentration of bilirubin in blood chemistry results should be also considered. Having considered the examinations and test results, the Sponsor will decide whether to approve such a patient for the study. If it is known that the patient had hepatitis B infection in the past, an additional examination may be performed along with the main examination (blood samples for HBsAg, anti-HBcor total, anti-HBcor-IgM and blood samples for qualitative PCR to HBV DNA are taken on the same day).

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	5. Blood chemistry abnormalities appearing as: a) creatinine > 2 × upper limit of normal (ULN) at screening; b) ALT, AST or alkaline phosphatase > 2.5 × ULN at screening; c) bilirubin > 1.5 × ULN at screening; 6. Leukocyte count < 3.0 × 10^9/L; absolute neutrophil count < 2.0 × 10^9/L; platelet count < 100 × 10^9/L, or hemoglobin < 90 g/L according to complete blood count at screening. 7. Any psychiatric conditions including severe depressive disorders and/or any history of suicidal thoughts or suicidal attempts[7]. 8. Signs of clinically significant depression (Beck's score ≥ 16 at screening). 9. Alcohol or substance abuse. 10. Tuberculosis now or in the past. 11. Latent TB infection (positive results of the Diaskintest[8], QuantiFERON test or T-spot). 12. Confirmed by source documentation and ongoing at screening, concurrent diseases that may increase the risk of adverse events during the study therapy or affect the evaluation of psoriasis symptoms (mask, enhance or alter the symptoms of psoriasis,

The patient with anti-HCV antibodies can be included in the study if all of the following conditions are met: negative qualitative PCR results for HCV RNA (this test is performed only if anti-HCV antibodies are detected); no abnormalities (increased transaminases or bilirubin levels) found in blood chemistry; the Infectious Disease Specialist provides a documented conclusion that the patient has no HCV/cured HCV; and the Sponsor approves the enrollment of this patient. If it is known that the patient had HCV infection in the past, an additional examination may be performed along with the main examination (blood samples for anti-HCV and blood samples for qualitative PCR for HCV RNA are taken on the same day).

The patient who has a positive test for syphilis can be included in the study at the discretion of the Sponsor if the Dermatology/Venereology Specialist provides a documented report that the patient has no syphilis/cured syphilis. An additional examination may be required to confirm the diagnosis (at the discretion of the Dermatology/Venereology Specialist).

[7] This exclusion criterion can be confirmed or rejected on the basis of medical records or as told by the patient. Patient's medical history that can, in the opinion of the investigator, jeopardize the patient or affect his/her ability to follow the protocol must be carefully evaluated.

[8] TB diagnostics can be performed with the skin test (Diaskintest) or blood test (QuantiFERON/T-spot). QuantiFERON/T-spot can be repeated once. Upon reconciliation with the Sponsor, the patient with uncertain Diaskintest/QuantiFERON/T-spot results can be enrolled in the study if the TB Specialist confirms in written that the patient has no TB infection, and the patient shows no signs of active TB according to the chest X-ray performed any time within 3 months before signing the ICF or during the screening. The Diaskintest results are valid if the test was performed within 3 months before signing the ICF.

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	or cause clinical or laboratory/instrumental symptoms similar to those of psoriasis): • Active inflammatory diseases or aggravation of chronic inflammatory diseases other than psoriasis; • Functional class III-IV stable angina of effort, unstable angina or a history of myocardial infarction within 1 year before signing the ICF; • Moderate to severe cardiac failure (NYHA class III-IV); • Treatment-resistant hypertension[9]; • Severe asthma, a history of angioedema; • Moderate to severe respiratory failure, grade 3/4 chronic obstructive pulmonary disease; • Diabetes mellitus with inadequate glycemic control, i.e. if HbA1C[10] level is ≥ 8% (to be valid, results should be obtained at screening or within 3 months before signing the ICF); • Thyrotoxicosis persisting despite thyrostatic drugs or hypothyroidism not compensated with thyroid hormone drugs[11]; • Systemic autoimmune diseases (including but not limited to systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, non-specific ulcerative colitis, systemic scleroderma, inflammatory myopathy, mixed connective tissue disease[12], overlap syndrome, etc.); • Any other underlying conditions (including but not limited to metabolism, hematology, renal, hepatic, pulmonary, neurological, endocrine, cardiac, and gastrointestinal disorders; infections) that, in the opinion of the Investigator, may affect the course of psoriasis, affect the assessment of its symptoms, or put the patient using the study therapy at unacceptable risk. 13. Malignancies with less than 5 years of remission.

[9] Treatment-resistant arterial hypertension is defined as blood pressure above the target range despite the concurrent use of a combination of three anti-hypertensive drugs of different classes, necessarily including a diuretic, and non-medication methods (salt-free diet, controlled physical exercise).
[10] Glycated hemoglobin is measured only in patients with suspected/diagnosed diabetes mellitus.
[11] In case of a history of thyroid disorders with thyrotoxicosis or hypothyroidism, the patient can participate in the study if he/she has laboratory confirmation of euthyroidism within 3 months before signing the ICF, and no symptoms developing during therapy with stable doses of antithyroid drugs/thyroid hormones for at least 4 weeks before signing the ICF.
[12] Signs/symptoms of psoriatic arthritis are not considered an exclusion criterion.

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	14. Known severe allergies (anaphylaxis or drug allergy to two or more drugs). 15. Known allergy or intolerance to monoclonal antibody drugs (murine, chimeric, humanized, or fully human) or any other components of the test drug or comparator. 16. Major surgery within 30 days before the screening, or a major surgery being scheduled at any time during the study. 17. Severe infections (including those that required hospitalization or parenteral antibacterial/antimycotic/antiprotozoal agents) within 6 months before signing the ICF. 18. Use of systemic antibacterial/antimycotic/antiprotozoal agents within 2 months before signing the ICF. 19. More than 4 episodes of respiratory infections within 6 months before signing the ICF. 20. Episodes of systemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, etc.) within 6 months before signing the ICF. 21. History of epileptic attacks or seizures. 22. Any concurrent diseases during which, in the Investigator's opinion, the study therapy can harm the patient. 23. Pregnancy, breastfeeding or planning for pregnancy while participating in the study. 24. Participation in any other clinical study within 3 months before signing the ICF or simultaneous participation in other clinical studies. 25. Patients who have been already randomized in the study but then withdrawn due to any reasons cannot be included in the study.
Study therapy	**Main treatment period (Week 0 through Week 54):** In this study period patients will be distributed to three arms: • **Arm 1:** Patients in this arm (85 subjects) will receive BCD-085 120 mg (two subcutaneous injections, 60 mg in 1.0 mL each) once a week during the first 3 weeks (induction) and then once every 2 weeks through Week 10. Thus, the investigational product will be administered on Day 1 of Week 0, Week 1, Week 2, Week 4, Week 6, Week 8, and Week 10.

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	• **Arm 2:** Patients in this arm (85 subjects) will receive BCD-085 120 mg (two subcutaneous injections, 60 mg in 1.0 mL each) once a week during the first 3 weeks (induction) and then once every 4 weeks through Week 10. Thus, the investigational product will be administered on Day 1 of Week 0, Week 1, Week 2, Week 6 and Week 10. To maintain the study blind, patients of this arm will receive placebo (2 injections) on Day 1 of Week 4 and Week 8. • **Arm 3:** Patients of this arm (43 subjects) will receive placebo (2 subcutaneous injections of placebo, 1.0 mL each) on Day 1 of Week 0, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10. On Week 12, the treatment efficacy will be assessed with a PASI 75 score, and the treatment will be **unblinded**. Patients from Arms 1 and 2 will be given BCD-085 once every 4 weeks. Patients from Arm 3 will receive BCD-085 as follows: ✓ Induction: Weeks 12, 13, and 14, once a week; ✓ Weeks 18 through 50: once every 4 weeks. Therefore, there will be 3 arms even after unblinding, and patients will receive BCD-085 according to the regimens described below: a) Patients in Arm 1 will receive BCD-085 120 mg (2 SC injections of 60 mg each) once every 4 weeks starting from Week 14 and through Week 50. b) Patients in Arm 2 will receive BCD-085 120 mg (2 SC injections of 60 mg each) once every 4 weeks starting from Week 14 and through Week 50. c) Patients in Arm 3 will receive BCD-085 120 mg once a week at Weeks 12, 13, 14, then once every 4 weeks (Weeks 18, 22, 26, 30, 34, 38, 42, 46, 50). **Extension study period (from Week 54 through Week 154 for Arms 1 and 2, through Week 166 for Arm 3):**

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	During **the extension study period** all patients who achieved PASI 75 at Week 52 will receive BCD-085 120 mg once every 4 weeks: a) Patients from Arm 1 will receive BCD-085 from Week 54 through Week 154. b) Patients from Arm 2 will receive BCD-085 from Week 54 through Week 154. c) Patients from Arm 3 will receive BCD-085 from Week 54 through Week 166. Patients who failed to achieve PASI 75 at Week 52 will be withdrawn from the study. In Arm 3, treatment will be extended by 12 weeks so that the total treatment duration in all arms can be 154 weeks. During the main treatment period (during the first 12 weeks of the study), patients from Arm 3 receive placebo, so the treatment period for these patients is extended to 166 weeks. Regardless of the arm where the patient is assigned to, during the main study period (Week 0 through Week 54) SC injections will be performed by an authorized member of the study team at the study site (except for the injection on Week 54). At Week 54 patients will be trained on how to self-inject the investigational product. If necessary, the training can be repeated at any of the subsequent visits. During the extension study period (Week 54 through Week 154 for patients from Arms 1 and 2, Week 54 to Week 166 for patients from Arm 3), patients will self-inject the investigational product at home after receiving relevant training at the study site. Injections of the investigational product on visit dates will be performed by an authorized member of the study team at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154 (in Arms 1 and 2) or at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154, 166 (in Arm 3). The first self-injection of the investigational product at Week 54 will be performed under the supervision of an authorized member of the study team. Patients from Arms 1 and 2 will self-inject the

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	investigational product on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150, patients from Arm 3 – on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150, 158, 162. At each of visits from Week 54 to Week 146 (patients from Arms 1 and 2) and at each of visits from Week 54 to Week 154 (patients from Arm 3), BCD-085 will be dispensed to patients for self-administration at home at an amount sufficient until the next visit. Patients are not allowed to use phototherapy, systemic therapy for psoriasis and psoriatic arthritis (except for NSAIDs) and live vaccines while they are in the study. Patients may use topical glucocorticoids (of mild to moderate potency) on the face, underarm, and genitals Patients may also use topical moisturizers, emollients, oils, and salicylic acid ointments, topical antibacterial and/or antimycotic agents as needed. 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 examination including: • Baseline clinical characteristics and medical history, • Physical examination, • Blood pressure and wrist pulse, • Electrocardiography, • Chest X-ray[13] • Complete blood count, • Blood chemistry, • hs-CRP, atherogenicity index, apoB1/apoA1, • Glycated hemoglobin HbA1C (only for patients with confirmed diabetes mellitus), • Pregnancy test[14],

[13] Chest X-ray is performed according to the standards of the study site.
[14] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

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	• Assessment of the patient's infection status [Diaskintest® or blood testing for TB (QuantiFERON or T-spot)]; examination by the TB Specialist (required if the Diaskintest®/QuantiFERON/T-spot test results are uncertain), anti-HIV antibodies and p24 antigen [HIVAg/Ab Combo], HBs-antigen, anti-HBcor antibodies [IgG + IgM/ IgM], and anti-HCV antibodies, qualitative PCR for HCV RNA/HBV DNA (only if the patient tests positive for respective antibodies), consultation with the Infectious Disease Specialist (required only if the patient tests positive for anti-HBcor or anti-HCV antibodies), microprecipitation reaction, and a direct hemagglutination assay (*T. pallidum*), • Beck's depression inventory, • Psoriasis area and severity (PASI), including body surface area affected by psoriasis (BSA), • Nail Psoriasis Severity Index (NAPSI), • Static Physicians Global Assessment (sPGA), • Assessment of psoriatic arthritis (the 66/68 swollen/tender joint count), functional activity (HAQ-DI), disease activity (assessed by the physician and by the patient, VAS), patient assessment of pain (VAS), and markers of inflammation (C-reactive protein and ESR), • Itch severity (VAS), • DLQI questionnaire. To measure the efficacy of treatment in the timeframes specified by the Protocol, changes over time in the PASI, NAPSI, and sPGA scores, VAS scores for itch severity, assessment of psoriatic arthritis (ACR 20/50/70), and quality of life (DLQI score) will be evaluated. To visualize the efficacy measures during the study, photographs of each patient will be taken on PASI assessment visits. For safety evaluation, the following will be closely monitored: all general disorders (including fever and flu-like syndrome), abnormal vital signs (blood pressure and wrist pulse), infectious complications, abnormal laboratory values (CBC results: hemoglobin, erythrocytes, platelets, leukocytes including changes in the leukocyte differential, ESR; blood chemistry: glucose, total

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	bilirubin, ALT, AST, total protein, creatinine; urinalysis), assessment of cardiovascular risks (hs-CRP, atherogenicity index, apoB1/apoA1 ratio), cardiac disorders (ECG), lung disorders (chest X-ray). In some cases, to rule out tuberculosis or neoplasms that emerged during the study treatment, chest computed tomography can be done at the discretion of the TB Specialist. For immunogenicity assessment, blood samples will be drawn from the patients and analyzed for binding and neutralizing anti-BCD-085 antibodies.
Total study duration	The expected duration of the study is 65 months, which includes patients' recruitment (up to 12 months), treatment period, follow-up period, and data collection and statistical processing. The expected duration of each subject's participation in the study, including the screening period, active study phase and follow-up period, is about 162 weeks (for patients from Arms 1 and 2) or 174 weeks (for patients from Arm 3).
Assessment of efficacy	**Primary endpoint:** • Proportion of patients who achieved PASI 75 at Week 12, by study arms. **Secondary endpoints in the main treatment period (Week 0 to Week 54):** • Proportion of patients who achieved PASI 75/90/100 at Weeks 8, 16, 24, 42 and 52, by study arms. • Proportion of patients with sPGA score 0 or 1 at Weeks 8, 12, 16, 24, 42, and 52. • Proportion of patients with sPGA score 0 at Weeks 16, 24, 42, and 52. • Relative change from baseline in PASI score at Weeks 8, 12, 16, 24, 42 and 52. • Change from baseline in itch severity measured with visual analog scale (0 mm to 100 mm) at Weeks 1, 12, 24, and 52. • Change from baseline in Nail Psoriasis Severity Index (NAPSI) score at Week 12, 24, and 52. • Change from baseline in Dermatology Life Quality Index (DQLI) score at Weeks 8, 12, 24, 42, and 52.

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	• Proportion of patients with DLQI score 0 or 1 at Weeks 24, 42, and 52. • Proportion of patients (among those with psoriatic arthritis) who achieved an ACR20/50/70 at Weeks 12, 24, and 52. **Efficacy endpoints during the extension study period (Week 54 through Week 166)** • Proportion of patients who maintained PASI 75/90/100 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085. • Proportion of patients who maintained sPGA 0-1 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085. • Proportion of patients who maintained sPGA score 0 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085. • Proportion of patients who maintained DLQI score 0-1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085. • Time to loss of PASI 75/90/100, sPGA 0-1/sPGA 0, DLQI 0-1 response during the treatment with BCD-085. • Proportion of patients who maintained ACR 20/50/70 response (among patients with psoriatic arthritis) after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085. • Proportion of patients who achieved PASI 75/90/100 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085. • Proportion of patients with sPGA score 0 or 1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of the treatment with BCD-085. • Proportion of patients who achieved sPGA score 0 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.

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	• Change from baseline in itch severity measured with visual analog scale (0 mm to 100 mm) after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085. • Change from baseline in Nail Psoriasis Severity Index (NAPSI) score after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085 (among patients with nail psoriasis at baseline). • Proportion of patients who achieved DLQI score 0 or 1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085. • Change from baseline in Dermatology Life Quality Index (DQLI) score after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
Assessment of safety	**Secondary endpoints:** • Proportion of patients who developed AEs/SAEs. • Proportion of patients who developed injection site reactions. • Proportion of patients who developed Grade 3/4 AEs/SAEs. • Proportion of patients who discontinued the study due to AEs and/or SAEs. • Exposure adjusted incidence rate of AEs/SAEs during the extension study.
Immunogenicity endpoints	• Proportion of patients with anti-drug antibodies (binding/neutralizing).
Statistical analysis	**Calculation of sample size** Two independent hypotheses will be tested during the study: 1. The main study hypothesis (stating the non-inferiority of BCD-085 Q4W vs. BCD-085 Q2W) will be tested at the significance level of 0.05; 2. The hypothesis stating the superiority of BCD-085 in different dosing regimens over placebo will be tested at the significance level of 0.05. The sample size required to run the study was calculated on the basis of the literature data on clinical efficacy. During study

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	planning, the hypothesis stating that BCD-085 Q4W is non-inferior to BCD-085 Q2W (H_0:$\varepsilon \leq \delta$, H_1:$\varepsilon > \delta$, where ε is the true difference in the rate of the efficacy variable between the arms, δ is the non-inferiority margin) was tested with the following error values: type I error of 5% (α=0.05), type II error of 20% (β=0.2), power of test of 80%. The efficacy criterion to calculate the sample size was PASI 75 rate at Week 12 in each arm. During study planning, the hypotheses stating that BCD-085 Q4W and BCD-085 Q2W are superior to placebo (H_{01}:$\varepsilon_{2w} \leq \delta$, H_{11}:$\varepsilon_{2w} > \delta$; H_{02}:$\varepsilon_{4w} \leq \delta$, H_{12}:$\varepsilon_{4w} > \delta$, where ε_{2w}, ε_{4w} is the true difference in the rate of the efficacy variable between the arms treated with BCD-085 Q2W and with BCD-085 Q4W, respectively, δ is the superiority margin for BCD-085 over placebo) were tested with the following error values: type I error of 5% (α=0.05), type II error of 20% (β=0.2), power of test of 80%. The efficacy criterion to calculate the sample size was PASI 75 rate at Week 12 in each arm. Thus, the study should include at least 193 patients (77 in each BCD-085 arm and 39 in the placebo arm). With a potential dropout rate of 10%, the study should involve 213 patients (85 patients in each BCD-085 arm and 43 patients in the placebo arm). **Methods of analysis** Statistical analysis will be performed using R programming language for statistical computing and SAS 9.4 environment. Normally distributed data will be analyzed using two-sample Student's t-test, Welch's t-test, and ANOVA. Non-normally distributed data will be analyzed using the Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test, and Friedman test. Categorical data will be processed using the Fisher's exact test, test for equality of frequencies, Pierson's χ^2 test with Yates correction, and Cochran-Mantel-Haenszel test. **Safety analysis** The safety analysis will include all patients randomized in the study [intent-to-treat (ITT) population]. **Efficacy analysis**

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	The efficacy will be assessed in the ITT (intent-to-treat) population, which includes all randomized patients. In addition, the efficacy can be evaluated in the PP (Per Protocol) population, which includes those patients who completed all visits without major protocol deviations. **Immunogenicity analysis** The immunogenicity analysis will include all patients who have received at least one dose of BCD-085 and had an evaluable (not missing/lost/spoiled) serum sample taken before the first dose of BCD-085 and at least one evaluable (not missing/lost/spoiled) serum sample taken at subsequent visits. 

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 2-3% of the population have 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 treatment-resistant forms of psoriasis have become more common, which significantly affects the patients' quality of life and leads, in some cases, to disability (about 1% of patients with psoriasis). This determines the social significance of psoriasis. According to Krueger et al., psoriasis, as a medical and social problem and a factor reducing quality of life, shares the first place with depression, cardiovascular disorders, and diabetes.

Today, psoriasis is considered incurable. However, advanced treatment options are able to significantly improve the clinical course of the disease.

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 to patients with mild psoriasis.

Phototherapy is an important option in the treatment of psoriasis. It includes photochemotherapy (PUVA), a combination of the UVA light and a photosensitizing agent taken orally; selective phototherapy, a combination of middle-wave and long-wave UV light; and narrow-band UVB therapy. The light is likely to exert its therapeutic effects by stimulating

production of cytokines with immunosuppressive effects, by enhancing expression of several molecules on the cell surface, and by inducing cell apoptosis.

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

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

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 minimal adverse effects.

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

- Inhibitors of tumor necrosis factor-alpha (adalimumab, certolizumab, etanercept, golimumab, and infliximab),
- Inhibitors of the similar p40 subunit of the proteins IL-12 and IL-23 (ustekinumab),
- Inhibitors of interleukin-17 or its receptor (secukinumab, ixekizumab, brodalumab).

The first biologics approved by the FDA for the treatment of psoriasis (2003) 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 long-term use of the drug [1].

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 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].

The recent findings suggest that interleukin-17 plays a key role in the development of psoriasis. Several drugs blocking this cytokine demonstrated high efficacy and favorable safety in a number of pivotal clinical studies [15-24]. The known interleukin-17-blocking drugs differ in the type of antibody used, the structure of the Fc fragment, and physicochemical properties. Secukinumab, for example, is a fully human antibody (Ig G1) that selectively binds to and neutralizes interleukin 17A (IL-17A). The FDA (U.S. Food and Drug Administration) and EMA (European Medicines Agency) approved secukinumab on the basis of four Phase 3 studies, including those in adults with moderate to severe plaque psoriasis diagnosed at least 6 months before the study initiation. All the studies were multicenter, placebo-controlled, and double-blind. They involved a total of 2403 patients. Most of the study subjects (> 50%) had clear or almost clear skin after 12 weeks of treatment with 300 mg secukinumab, which refers to at least 90% improvement of all symptoms as compared to baseline (PASI 90) [21-23]. In a more recent study (CLEAR; 679 patients), in which secukinumab was compared with ustekinumab, 44% of patients on secukinumab and 28% of patients on ustekinumab achieved PASI 100 at Week 16 of treatment [24].

Psoriasis is a common and socially significant chronic disease. Thus, development of drugs that block IL-17 signaling is a promising approach in searching for new highly effective and safe treatments for psoriasis.

1.1.2. Background information for studied therapy

Although the exact mechanism of psoriasis is unknown, the pathological process is thought to involve both innate and adaptive immune responses affecting keratinocytes and other skin cells such as fibroblasts, mast cells, and endothelial cells [2, 3, 4].

A psoriatic plaque becomes infiltrated with activated T-cells that produce a number of cytokines, i.e. interferon-gamma, tumor necrosis factor-alpha, interleukin-17 (17A), and interleukin-22 [2, 5, 6, 7]. Certain substances are produced by the dendritic cells (interleukin-23, interleukin-20, and TNF-α) and keratinocytes (CXCL8, CXCL1, CCL20) [3, 8, 9]. After the role of the cytokines in psoriasis has been demonstrated, a large number of studies have been initiated to investigate effects of blocking particular molecules. Results obtained in these studies suggest that interleukin-17 (produced by the T-cells in response to interleukin-23) plays a key role in skin damage [10].

Interleukin-17 exhibits significant pro-inflammatory activity *in vitro* and *in vivo*, can induce the synthesis of various inflammatory mediators (including TNF-α and interleukins 1, 6 and 8 (CXCL8) [29, 30, 31], and stimulates keratinocytes to produce various chemokines [26, 27, 28], thus promoting inflammation in psoriasis patients.

IL-17 blockade reduces the production of pro-inflammatory cytokines, secretion of chemokines by keratinocytes, and, therefore, suppresses the inflammation. The clinical effect is the reduction of the pathological processes in the psoriatic plaque and limiting the area of the affected skin. Thus, blockade of this cytokine in patients with psoriasis is thought to be a promising and justified therapeutic approach.

It is interesting that available effective treatments affect either IL-23 or IL-23-induced IL-17. Ustekinumab suppresses IL-23 and IL-12 (yet several small studies have shown that IL-12 inhibition has a little impact on the overall efficacy of ustekinumab) [10]. The clinical efficacy of other psoriasis treatments (cyclosporine, phototherapy, etanercept, TNF inhibitors) positively correlates with the suppression of interleukin-17 [11, 12, 13, 14]. These data confirm the essential role that interleukin-17 plays in the pathogenesis of psoriasis and justify the feasibility of developing clinically effective drugs affecting this signal pathway.

In 2012, the data were published illustrating the clinical effect of monoclonal antibodies specifically interacting with IL-17 (or IL-17 receptor) in patients with moderate to severe psoriasis. In clinical studies, the proportion of PASI 75 responders after 12 weeks of treatment was up to 89.7% in the test drug arms and up to 9% in the placebo arm [15-24]. Moreover, the new drugs were shown superior to such approved and effective medications as etanercept and ustekinumab [16, 18, 24].

JSC BIOCAD has developed an original anti-IL-17 monoclonal antibody (BCD-085) that has several advantages. [redacted] As of now, a full range of non-clinical investigations and phase I and II clinical studies has been conducted with BCD-085. In the non-clinical program, the drug showed *in vitro* and *in vivo* potency, low immunogenicity, and low toxicity, and was well tolerated by the animals. In the Phase I dose-escalation clinical study when single doses of BCD-085 were given subcutaneously to healthy volunteers, the pharmacokinetics of the drug was characterized, and its suitable tolerability and safety were demonstrated. Phase II clinical studies in patients with moderate to severe plaque

psoriasis and patients with active ankylosing spondylitis showed significant superiority of BCD-085 over placebo and its favorable safety profile.

Thus, the evidence available shows an apparent potential of developing BCD-085, which should result in a new highly-effective and safe treatment for psoriasis.

1.2. Name and description of the investigational products

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

1.2.1. Test drug

Trade name: not assigned.

Internal code: BCD-085.

[redacted]

[redacted]

1.2.2. Placebo

[redacted]

1.2.3. Labeling of the investigational products

Labeling during the blinded treatment period

The treatment will be blinded until Week 12, so both investigational products will be labeled the same way during this period.

According to Article 46 of Federal Law 61-FZ "On the Circulation of Medicines" of April 12, 2010 and regulatory requirements of the Republic of Belarus, the primary packaging of the investigational product will contain the following information (printed in Russian, in the easily readable font):

- BCD-085/placebo,
- Lot No,
- Date of manufacture,
- Shelf life,
- Dosage.

The secondary packaging will contain the following information (printed in Russian, in the easily readable font):

- BCD-085/placebo,
- Manufacturer's name: JSC BIOCAD, Russia,
- Lot No,
- Date of manufacture,
- Shelf life,
- Route of administration,
- Dosage,
- Pharmaceutical form,
- Prescription status,
- Storage conditions,
- Cautionary labeling,
- Visit name.

Both the primary and secondary packaging will also have the "For clinical studies only" label.

The secondary packaging also will contain the following information: protocol code, patient's identification number, date of injection.

Labeling during the open-label treatment period

The period from Week 12 to Week 158 (for Arms 1 and 2) or from Week 12 to Week 174 (for Arm 3) is open-label, so no treatment blinding is required.

According to Article 46 of Federal Law 61-FZ "On the Circulation of Medicines" of April 12, 2010 and regulatory requirements of the Republic of Belarus, the primary packaging of the investigational product will contain the following information (printed in Russian, in the easily readable font):

- Name of the investigational product (BCD-085),
- Batch,
- Date of manufacture,
- Shelf life,
- Dosage.

The secondary packaging will contain the following information (printed in Russian, in the easily readable font):

- Name of the investigational product (BCD-085),
- Manufacturer's name: JSC BIOCAD, Russia,
- Batch,
- Date of manufacture,
- Shelf life,
- Route of administration,
- Dosage,
- Pharmaceutical form,
- Prescription status,
- Storage conditions,
- Cautionary labeling.

Both the primary and secondary packaging will also have the "For clinical studies only" label.

The secondary packaging also will contain the following information: protocol code, patient's identification number, date of injection.

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 antibody selectively targeted the human IL-17A antigen and had a high binding constant [redacted]

[redacted]

1.3.1.2. Non-clinical pharmacodynamics

[redacted]

[redacted]

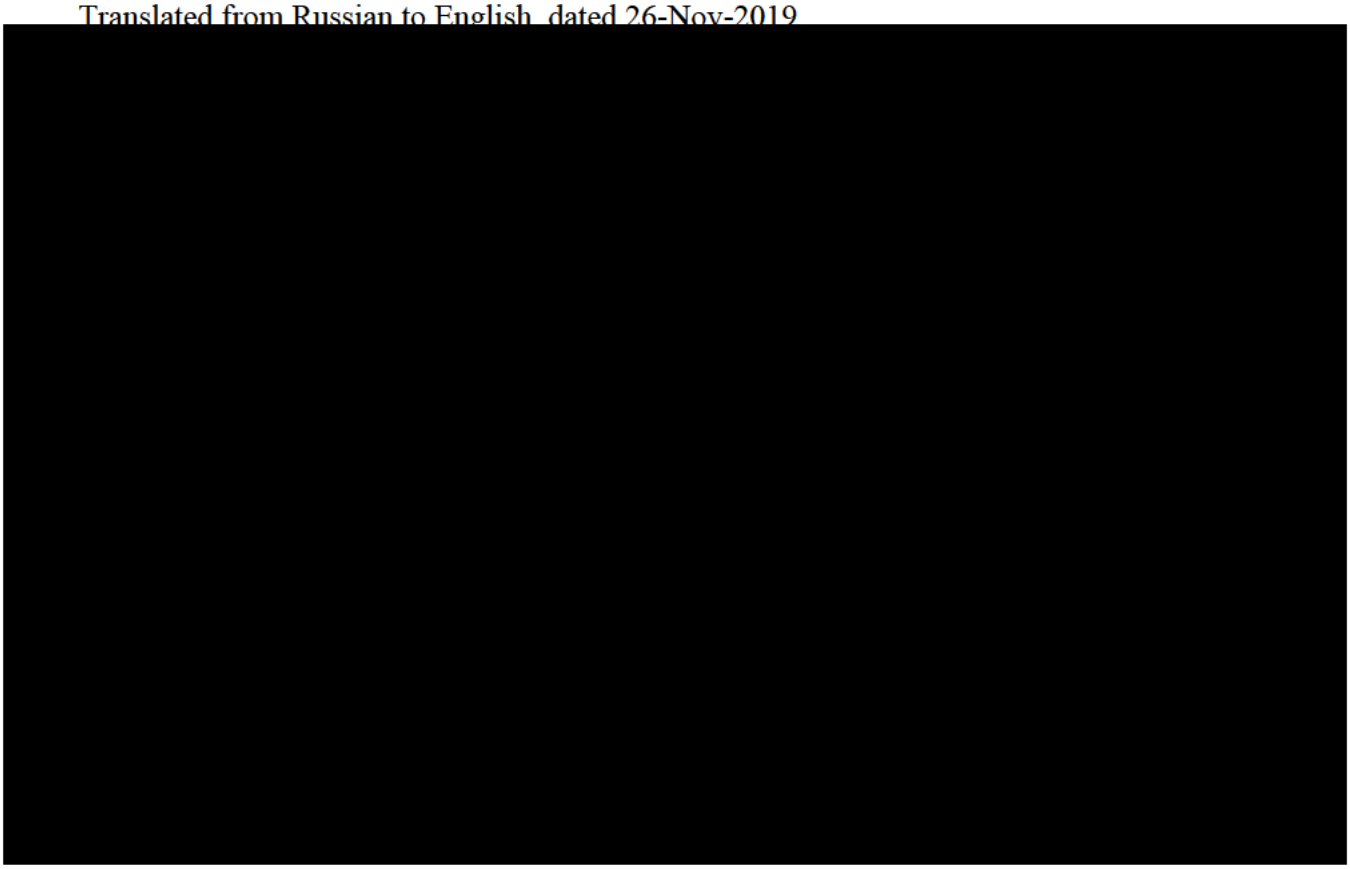
[redacted]

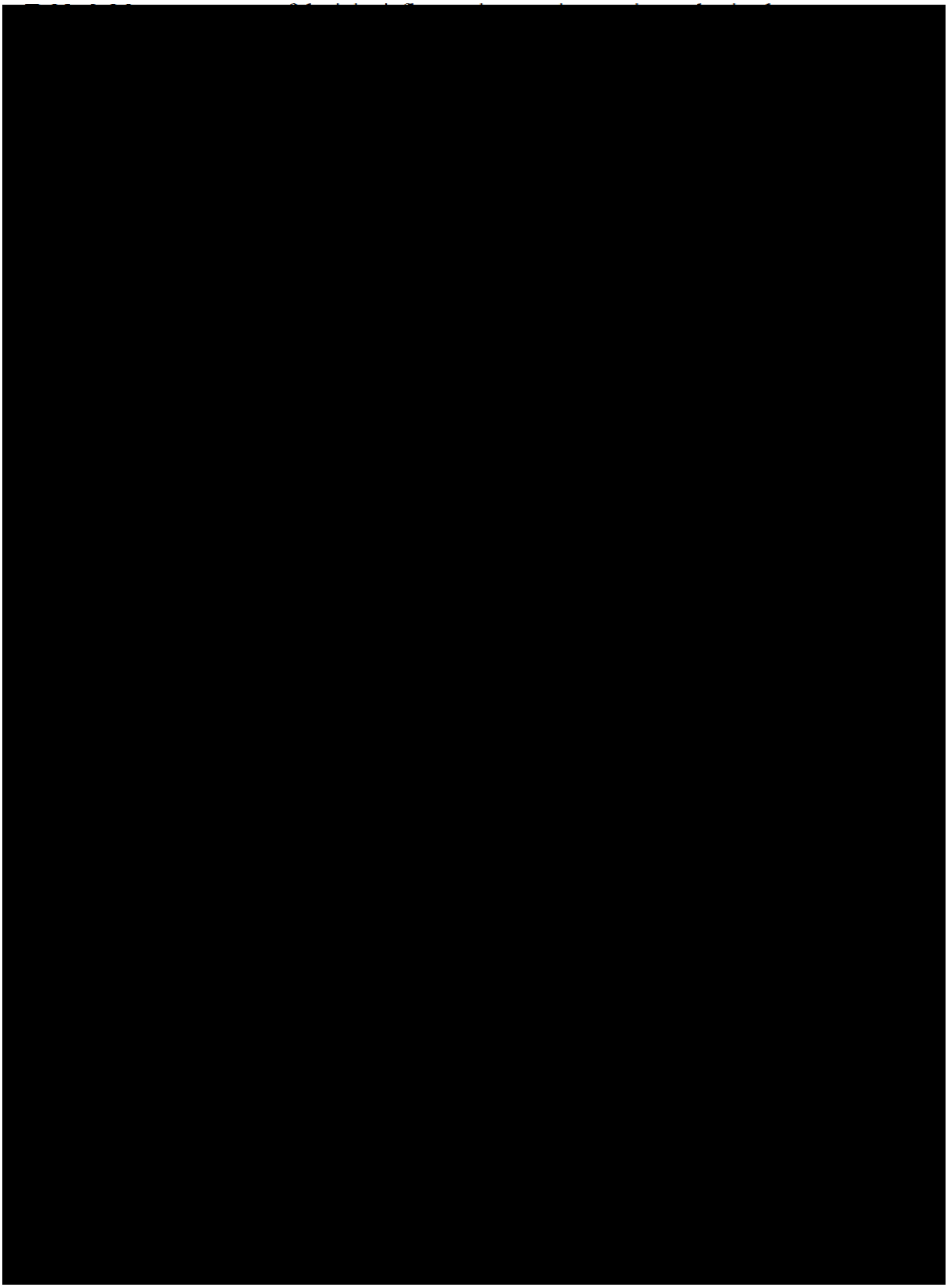
[redacted]

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

The pharmacodynamics of the anti-IL-17 monoclonal antibody was studied in the collagen-induced arthritis model 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 after 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 involved joint surface was lower than that in the controls at all time points. The most pronounced effect was observed in animals treated with the lowest dose (4.0 mg/kg). The percentage of involved joint surface was significantly lower than that in the controls starting from Week 4 of the experiment (counted starting from the first injection) and until the end of the experiment. For animals dosed with 8.0 mg/kg BCD-085, significant differences were seen only at the end of the experiment.

Examination of the metacarpophalangeal and metatarsophalangeal joints showed the changes typical for the initial signs of arthritis in the placebo-dosed animals. Disappearance of the *lamina splendens* was observed in all animals. The surface zone opened directly in the joint cavity as a homogeneous matrix. Selective staining with toluidine blue revealed swelling and slight in the surface zone, and metachromasia on the surface detecting focal disappearance of acidic glycans. Signs of apoptosis, hypertrophy, and proliferation were seen in the chondrocytes. The synovial membrane was moderately swollen and plethoric with insignificant signs of proliferation. No lymphoplasmacytic proliferation was observed. The subchondral plate and underlying bone trabeculae were normal.

Disappearance of the *lamina splendens* was observed in one animal (No. 3) from the 4.0 mg/kg group. In other cases, the cartilage remained intact, and the synovial membranes had no signs of damage or inflammation. No proliferation of synoviocytes was observed.

Animals from the 8.0 mg/kg group had intact cartilages; no disruption of the surface pattern was seen, and the ratio between the matrix and cellular structure was normal. The matrix and associated chondrocytes were organized in three appropriately oriented, well-ordered zones (superficial, central, and deep). The subchondral plate and underlying bone trabeculae were normal. The synovial membrane was normal with no signs of proliferation.

Repeated (once a week for 4 weeks) SC administration of BCD-085 to cynomolgus monkeys (*Macaca fascicularis*) was associated with a significant reduction of inflammation and degeneration induced by two injections of collagen. These results were supported by the histological findings as well.

1.3.1.2.3. Repeated-dose pharmacokinetics study of BCD-085

Pharmacokinetics of BCD-085 was studied in healthy cynomolgus monkeys (*Macaca fascicularis*) after multiple SC injections at doses of 2 mg/kg, 8 mg/kg, and 40 mg/kg (18 animals).

The repeated-dose PK parameters were investigated with 2.0 mg/kg, 8.0 mg/kg, and 40.0 mg/kg doses. The highest dose used in this study (40 mg/kg) equaled 10 doses that showed the maximum anti-inflammatory effect in the PD study performed in collagen-induced arthritis (CIA) model. This meets requirements stated in both Russian and international regulations[15].

The animals were divided into three groups according to drug doses assigned.

BCD-085 was administered subcutaneously in the withers once a week for 25 weeks. This administration mode corresponds to one recommended for clinical use. The following doses were used in the study: 2 mg/kg, 8 mg/kg, and 40 mg/kg. The injection volume was 0.8 mL/kg. BCD-085 was administered at a dose of 2.5 mg/mL in the minimum-dose group, 10.0 mg/mL in the medium-dose group, and 50.0 mg/mL in the maximum-dose group.

Serum levels of BCD-085 were evaluated by means of ELISA. Experimental data were used to calculate the $AUC_{0\text{-}168}$ (an integral index characterizing the changes in the drug concentration after the first injection during the dosing period of 168 h) and $AUC_{ss168\ (4032\text{-}4200)}$ (steady-state AUC referring to the 168-h dosing interval). In addition, the accumulation ratio was calculated as the ratio of $AUC_{ss168\ (4032\text{-}4200)}$ to $AUC_{0\text{-}168}$. The values of $AUC_{0\text{-}168}$ and $AUC_{ss168\ (4032\text{-}4200)}$ were dose-proportional, while the values of half-life period did not depend on the dose of BCD-085. This suggested the linear pharmacokinetics of BCD-085.

The accumulation ratio did not depend on the dose and was similar across the groups. The accumulation ratio was 2.35 with BCD-085 2.0 mg/kg, 2.68 with BCD-085 8.0 mg/kg, and 2.17 with BCD-085 40.0 mg/kg.

[15] Guidelines for non-clinical studies of medicinal products (edited by A.N. Mironova, M. Federal State Budgetary Institution Scientific Center for Expert Evaluation of Medical Products of the Ministry of Healthcare of the Russian Federation, 2012, in two volumes); Guideline on experimental (non-clinical) investigation of new pharmacological compounds // M. - 2005; Guidelines on evaluation of medicinal products (edited by Mironova A.N., M. Federal State Budgetary Institution Scientific Center for Expert Evaluation of Medical Products, 2014, in two volumes); Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology. World Health Organization – 2013; ICH Harmonised Tripartite Guideline Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1) – 2011

The PK parameters were calculated based on the concentrations of BCD-085 in the serum of all experimental animals.

1.3.1.2.4. Single-dose toxicity of BCD-085

The following doses of BCD-085 were used in a single-dose SC toxicity study: 8.0 mg/kg, 40.0 mg/kg, and 80.0 mg/kg. The minimum dose used in this study is equivalent to the expected therapeutic dose in humans with the 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 involved 16 male and female monkeys (*Macaca fascicularis*) with body weight from 3.0 kg to 7.0 kg:

1. BCD-085 8 mg/kg (2 males and 2 females)
2. BCD-085 40 mg/kg (2 males and 2 females);
3. BCD-085 80 mg/kg (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);
- Changes in pelage (piloerection, alopecia, pelage color);
- Eye changes (tearing, discharge);
- Effects on animal behavior.

The study results showed that BCD-085 in the tested doses did 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 limited volume that could be injected). The general health of animals was satisfactory throughout the entire experiment; no body weight loss was registered. CBC parameters and blood chemistry markers of the liver and urinary system 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 (40 mg/kg) and high (80 mg/kg) 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 BCD-085 40.0 mg/kg and 80.0 mg/kg 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 30 monkeys (*Macaca fascicularis*). BCD-085 was administered subcutaneously in the withers once a week for 25 weeks. This administration mode corresponds to one recommended for clinical use. The following doses were used in the study: 2 mg/kg, 8 mg/kg, and 40 mg/kg. The injection volume was 0.8 mL/kg. BCD-085 was administered at a dose of 2.5 mg/mL in the minimum dose group, 10.0 mg/mL in the medium-dose group, and 50.0 mg/mL in the maximum dose group. The highest dose used in this study (40 mg/kg) equaled 10 doses that showed the maximum anti-inflammatory effect in the PD study performed in collagen-induced arthritis (CIA) model. This meets requirements stated in both Russian and international regulations[16]. The maximum concentration of BCD-085 used in this study was higher than the concentration planned to be used in clinical studies.

The recovery period (drug-free) was 8 weeks. The animals were divided into 5 groups according to the doses of the test drug and the time when they were euthanized: the minimum dose group (2 mg/kg, 1 male and 1 female euthanized at the end of the recovery period), the medium-dose group (8 mg/kg, 1 male and 1 female euthanized at the end of the recovery period), the maximum dose/main group (40 mg/kg, 3 males and 3 females euthanized after 25 doses of BCD-085), the maximum dose/satellite group (40 mg/kg, 3 males and 3 females euthanized at the end of the recovery period), and the placebo control group (3 males and 3 females euthanized at the end of the recovery period).

[16] Guidelines for non-clinical studies of medicinal products (edited by A.N. Mironova, M. Federal State Budgetary Institution Scientific Center for Expert Evaluation of Medical Products of the Ministry of Healthcare of the Russian Federation, 2012, in two volumes); Guideline on experimental (non-clinical) investigation of new pharmacological compounds // M. - 2005; Guidelines on evaluation of medicinal products (edited by A.N. Mironova, M. Federal State Budgetary Institution Scientific Center for Expert Evaluation of Medical Products, 2014, in two volumes); Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology. World Health Organization – 2013; ICH Harmonised Tripartite Guideline Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1) – 2011.

The toxicological profile of the study drug was assessed by using common experimental methods recommended for non-clinical studies.

The following parameters were monitored during the study: motor activity, vegetative reactions, pelage, eye changes, nasal mucosa, oral mucosa, stool, appetite, breathing pattern, urinary function, and cellular profile of peripheral blood. Also, the effects of BCD-085 on the following were assessed: 1) blood clotting system; 2) protein, carbohydrate metabolic and enzymatic functions of the liver (by means of blood chemistry – liver function tests, total bilirubin, cholesterol, protein, triglycerides, and glucose), 3) urinary system (urinalysis and blood chemistry: urea, creatinine, sodium, and potassium); 4) cardiovascular system (ECG); and 5) central nervous system.

The animals were euthanized according to the standard protocol for the postmortem examination of the viscera.

The animals tolerated well the anti-IL-17 monoclonal antibody. No body weight loss, behavioral changes or thermogenic reactions were registered in any experimental animal over the entire study. Multiple injections of BCD-085 (2 mg/kg, 8 mg/kg, or 40 mg/kg) did not change major CBC or clotting parameters, did not affect the functions of the liver, urinary or cardiovascular systems.

No changes in autonomic reactions (pupil diameter, eye slit size, salivation, involuntary defecation, urination, increased diuresis) were observed. The test drug did not affect pelage (caused no piloerection, alopecia, or changes in pelage color), did not lead to any eye changes (tearing, discharge), did not affect nasal or oral mucosa. Throughout the entire study, no drug effects on animal appetite were observed (food or water consumption). Neither did repeated administration of the drug affect the stool of the animals. The daily clinical examination did not reveal any effects of BCD-085 on breathing pattern, motor activity, or sociability of the animals.

The histological findings suggested that the test drug caused no local reactions in the administration site.

The gross examination did not reveal any toxic effects of BCD-085 on organs or organ systems. In most cases, the morphological structure of the internal organs was consistent with animals' age and normal histology. Most changes were seen also at baseline or could develop as spontaneous abnormalities during the study, which can be expected in captive-held animals.

The toxicity study of BCD-085 (an anti-Il-17 mAb product, JSC BIOCAD) showed that the test drug produced no toxic effect on any major organs or organ systems of experimental

animals upon repeated-dose weekly subcutaneous administration over 25 weeks. The no-observed-adverse-effect-level (NOAEL) established in this study corresponded to the highest dose of BCD-085 (40 mg/kg).

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

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

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

Histological examination of the tissues taken after necropsy of animals in the main max dose group showed that BCD-085 40 mg/kg administered subcutaneously for 25 weeks did not produce any local intolerance in cynomolgus monkeys. Histological examination did not show any changes in the injection sites or draining lymph nodes.

1.3.1.2.7. Immunotoxicity of BCD-085

Repeated-dose immunotoxicity was studied using two doses of BCD-085: 8.0 mg/kg and 40.0 mg/kg. The experiment was conducted in 9 male monkeys (*Macaca fascicularis*) of 3.0 kg to 7.0 kg. The animals were divided into three groups depending on the dose/drug administered:

1. BCD-085 8.0 μg/kg (3 males);
2. BCD-085 40.0 μg/kg (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 showed that the test drug did not alter the subpopulation ratio.

An assessment of drug effects on humoral immunity was one of the main parts of immunotoxicity study.

The obtained results evidence that repeated SC administration of BCD-085 did not alter the levels and balance of immunoglobulins *M, G, A, 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 BCD-085 8.0 mg/kg and 40.0 mg/kg in cynomolgus monkeys produced no immunotoxicity in the said experimental settings.

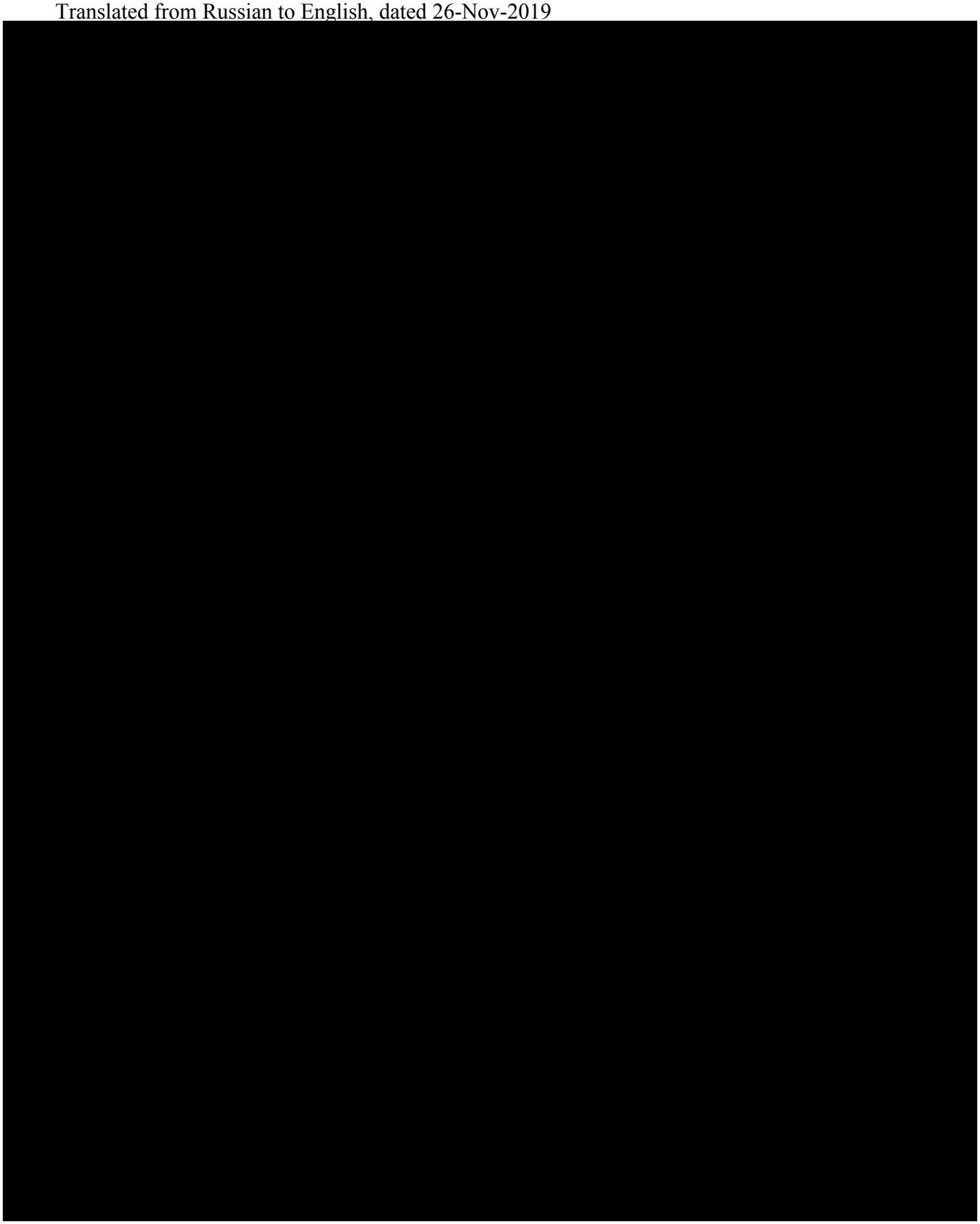
[redacted]

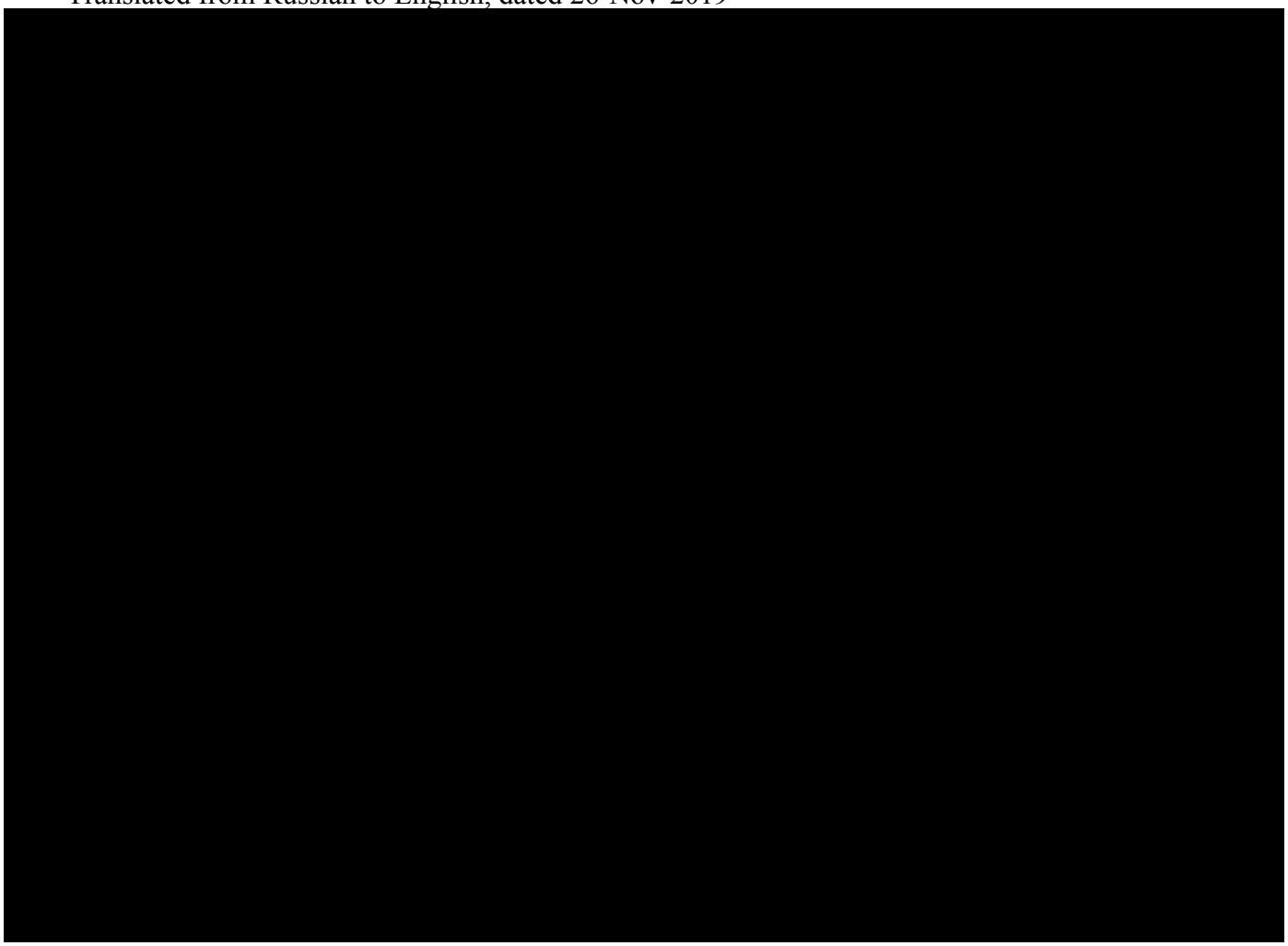
[redacted]

1.3.1.2.11. 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]





[redacted]

1.3.1.2.12. 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 2 mg/kg, 8 mg/kg, and 40 mg/kg (18 animals).

The animals were divided into three groups according to drug doses assigned.

BCD-085 was administered subcutaneously in the withers once a week for 25 weeks. This administration mode corresponds to one recommended for clinical use. The following doses were used in the study: 2 mg/kg, 8 mg/kg, and 40 mg/kg. The injection volume was 0.8 mL/kg. BCD-085 was administered at a dose of 2.5 mg/mL in the minimum dose group, 10.0 mg/mL in the medium-dose group, and 50.0 mg/mL in the maximum dose group.

The potential effect of binding anti-BCD-085 antibodies on the PK parameters of the drug was assessed. Experimental findings confirmed that no animals developed anti-drug binding antibodies in any test group.

1.3.2. Clinical studies

By the time this Protocol was written, a Phase I clinical study was completed that investigated the safety, tolerability, and pharmacokinetics of single ascending doses of BCD-085. The results of this study are described below. BIOCAD also completed Phase II studies of the efficacy and safety of BCD-085 given as repeated SC injections of different doses in patients with moderate to severe plaque psoriasis and patients with ankylosing spondylitis. Study results are presented in section 1.3.2.2.2. Efficacy and safety of BCD-085.

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

An open-label clinical study of the pharmacokinetics, tolerability, and safety of single ascending doses of BCD-085 in healthy volunteers 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 dose of BCD-085 0.05 mg/kg of body weight.
2. Cohort 02: 3 volunteers who received single SC doses of BCD-085 0.05 mg/kg of body weight.
3. Cohort 03: 3 volunteers who received single SC doses of BCD-085 0.25 mg/kg of body weight.
4. Cohort 04: 3 volunteers who received single SC doses of BCD-085 0.825 mg/kg of body weight.
5. Cohort 05: 3 volunteers who received single SC doses of BCD-085 1.25 mg/kg of body weight.
6. Cohort 06: 3 volunteers who received single SC doses of BCD-085 1.75 mg/kg of body weight.
7. Cohort 07: 3 volunteers who received single SC doses of BCD-085 2.25 mg/kg of body weight.
8. Cohort 08: 3 volunteers who received single SC doses of BCD-085 3.0 mg/kg of body weight.

The volunteers were included in the study one after another. At first, 1 volunteer was included in Cohort 01 and received a single subcutaneous dose of BCD-085 0.05 mg/kg (estimated starting safe dose). If the volunteer 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 (DLT) 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 complete blood count and blood chemistry) of grade 1 in 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 AST increased (1 event in Cohorts 05 and 06) and ALT increased (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 included 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 the

SAE) 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 concentration vs. time curve from drug 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 maximum concentration);
- $T_{½}$ (half-life period),
- 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 h to 211 h (on 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 to 22 days).

[redacted]

[redacted]

1.3.2.2. Efficacy and safety findings

1.3.2.2.1. Efficacy and safety of products targeting interleukin-17

Today, information is available on the efficacy of the closest analogs of BCD-085 that have a similar mechanism of action (ixekizumab, secukinumab, and brodalumab). The first two

[17]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.

products contain fully human monoclonal antibodies selective for interleukin-17, and the last one contains antibodies that target the IL-17 receptor.

A Phase II clinical study of ixekizumab included 142 patients with moderate to severe psoriasis, who were randomized to 5 arms: 150 mg, 75 mg, 25 mg, and 10 mg of ixekizumab, and placebo. The test drug/placebo was administered at Weeks 0, 2, 4, 8, 12, and 16. The primary endpoint set as the proportion PASI 75 responders 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].

Two Phase III pivotal clinical studies, UNCOVER-2 and UNCOVER-3, were conducted 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 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) were met in both studies with both regimens of ixekizumab therapy. In the UNCOVER-2 and UNCOVER-3 studies, the PASI 75 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 studies.

Adverse reactions	Placebo, n=360	Etanercept, n=739	IX4W, n=729	IX2W, n=734
Any treatment-emergent AE	44.2%	53.9%	57.5%	57.4%
SAE	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 heterodimeric IL-17A/F cytokine. In a 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/placebo 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 the response in all active 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 were 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 PASI 75 responders 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 PASI 75 responders and sPGA responders.

Table 6. Results from the AMAGINE-2 and AMAGINE-3 studies 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 maintained the PASI 75 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 studies during the induction phase (first 12 weeks) are listed in Table 7.

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

Adverse reactions	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%
SAE	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 infections	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 reactions	1.4%	2.0%	1.6%	1.5%

In November 2014, Amgen and AstraZeneca announced positive results from a Phase III study, 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 PASI 75 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 progression of the main disease, nasopharyngitis, and upper respiratory tract infections.

Another Phase II study [20] used different 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 demand ("start of relapse" regimen). During the induction phase (Week 12), the proportion of PASI 75 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 PASI 75 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%, by arms, 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 reactions	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%
SAE	1.8%	1.2%	2.1%	0.9%
Nasopharyngitis	8.0%	10.7%	13.8%	11.1%
Upper respiratory tract infections	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 infections	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 a favorable safety profile in the clinical studies.

1.3.2.2.2. Efficacy and safety of BCD-085

By the date of this Protocol, two Phase II studies (in patients with plaque psoriasis and patients with ankylosing spondylitis), and extension periods (treatment extension to 1 year) of these studies have been completed.

1.3.2.2.2.1. Results of the efficacy and safety study of BCD-085 in patients with psoriasis

The first Phase II study ("An International, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-finding Clinical Study of the Efficacy and Safety of Subcutaneous BCD-085 in Patients with Moderate to Severe Plaque Psoriasis") has now been completed. This study aimed at finding the optimal BCD-085 doses and treatment regimen for patients with moderate to severe plaque psoriasis and at investigating the efficacy, safety, and pharmacokinetics of BCD-085.

According to the approved Protocol, the study involved 120 adults with moderate to severe plaque psoriasis. Before being included in the active phase of the study, all patients underwent a screening examination (max duration: 28 days) to determine whether they met the eligibility criteria. When all screening procedures were completed and the Investigator qualified the patient eligible for the study, the patient was stratified by body weight (≤80 kg/≥81 kg), prior use of monoclonal antibodies for the treatment of psoriasis (MAb-treated/MAb-naive), current use of systemic non-biologics (yes/no), PASI score (<20/≥20), and signs of psoriatic arthritis (absent/present). After stratification, the patients were randomized 1:1:1:1 to four study arms (Arm 1: BCD-085 40 mg, Arm 2: BCD-085 80 mg, Arm 3: BCD-085 120 mg, Arm 4: placebo). Thus, the active period of the study involved the test drug/placebo injections given 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, and immunogenicity of BCD-085. Patients involved in the PK study (a limited population) attended 13 visits.

The treatment efficacy was assessed as a proportion of patients who achieved PASI 75 at Week 12 of treatment. The PASI 75 achievement was defined as at least 75% improvement in the overall PASI score at Week 12 versus baseline.

The efficacy population included 114 patients.

The analysis showed that BCD-085 in all tested doses was superior over placebo in patients with moderate to severe plaque psoriasis. Over 90% of patients in the high-dose arm (120 mg) responded to the treatment. Results for PASI 75 achievement are shown below.

Table 11. Assessment of the primary endpoint (achievement of PASI 75) in the Phase II study (Arm 1: BCD-085 40 mg, Arm 2: BCD-085 80 mg, Arm 3: BCD-085 120 mg, Arm 4: placebo).

Arm	Drug	Proportion of PASI 75 responders, n (%)	*P* value
1 (n=30)	BCD-085 (40 mg)	24 (80.0%)	**$P_1 < 0.0001$** **$P_2 < 0.0001$**
2 (n=30)	BCD-085 (80 mg)	25 (83.33%)	
3 (n=28)	BCD-085 (120 mg)	26 (92.86%)	
4 (n=26)	Placebo	6 (23.08%)	
Note: 1 – two-sided Fisher's exact test; 2 – two-sided Pearson's χ^2 test with Yates correction			

To prove the pre-specified hypothesis of BCD-085 being superior to placebo, the 95% CIs were derived for the difference in PASI 75 responses in the study arms (individual pair-wise comparisons were performed for placebo versus each BCD-085 arm). The hypothesis was accepted if the lower bound of the estimated 95% CI for the PASI 75 response rate was above the pre-specified margin of clinically non-meaningful differences (δ = 10% = 0.10). The results are provided below.

Table 12. Difference in PASI 75 rates in the arms, with the 95% CIs (Arm 1: BCD-085 40 mg, Arm 2: BCD-085 80 mg, Arm 3: BCD-085 120 mg, Arm 4: placebo).

Difference in PASI 75 rates		95% CI	*P* value[1]
Arms 1 and 4	56.92%	[31.72%; 82.13%]	**<0.0001**
Arms 2 and 4	60.25%	[35.69%; 84.83%]	**<0.0001**
Arms 3 and 4	69.78%	[47.28%; 92.28%]	**<0.0001**
Note: 1 - two-sided Pierson's χ^2 test with Yates correction			

This table shows that the lower bounds of the 95% CIs for all pair-wise comparisons (placebo versus each of BCD-085 arms) fell outside the pre-specified superiority margin (δ = 0.10). Thus, the hypothesis of BCD-085 being superior to placebo in patients with moderate to severe plaque psoriasis was accepted, and the primary study endpoint was achieved. It is important that the superiority of BCD-085 over placebo was proved for all tested doses (40 mg, 80 mg, and 120 mg).

Assessment of PASI 50/75/90 achievement and relative changes in the PASI score showed that PASI score in the BCD-085 arms decreased significantly over time, with this reduction being significantly more pronounced than that in the placebo arm. Although there were no significant differences among the BCD-085 arms, the absolute values demonstrated the dose-dependent nature of the response. The highest proportions of all types of PASI achievers at Week 12 were seen in the arm dosed with BCD-085 120 mg. Similar trends were seen for the changes in the BSA and the proportion of patients with sPGA 0 or 1.

The best response in terms of the NAPSI score and the itch severity was also seen with BCD-085 120 mg. Patients in this arm showed the best nail and itch improvement among all study arms.

The quality of life assessment demonstrated the opposite results for two scores (SF-36 and DLQI). The DLQI score decreased gradually and significantly with time (which indicates an improvement in the QoL) in the BCD-085 arms and did not change in the placebo arm, while the SF-36 score (physical component) at Week 12 improved significantly in the placebo arm (with no inter-arm differences detected at all time points), and the mental SF-36 component improved significantly in Arm 1 (inter-arm comparison detected the difference only at Week 12). These findings are likely to be explained by the fact that the SF-36 is a nonspecific questionnaire used to assess the QoL in patients with various pathologies. This questionnaire is not tailored to diseases of any particular organs or systems, which may result in certain difficulties when interpreting patient responses with regard to psoriasis. At the same time, the DLQI is a validated dermatology-specific instrument. Results obtained with the DLQI do not contradict the results obtained for other study endpoints.

BCD-085 was proved superior to placebo. The primary study goal was achieved. Although there were no differences between three doses of BCD-085, the best overall reduction in the signs/symptoms of psoriasis was detected in the BCD-085 120 mg arm.

The safety analysis included 117 patients. BCD-085 (all tested dose levels) demonstrated a favorable safety profile with adverse events not differing in nature and severity from those seen with placebo.

At least one AE/SAE was reported in 45.16% (14 of 31) of patients in Arm 1, 36.67% (11 or 30) of patients in Arm 2, 25.00% (7 of 28) of patients in Arm 3, and 39.29% (11 of 28) of patients in Arm 4 ($P = 0.443$, two-sided χ^2 test with Yates correction). AEs/SAEs were judged as related to the study treatment in 6 (19.35%) patients in Arm 1, in 3 (10.00%) patients in Arm 2, in

2 (7.14%) patients in Arm 3, and in 3 (10.71%) patients in Arm 4 (p=0.534, two-sided Fisher's exact test). The pairwise comparison of the overall frequency of AEs/SAEs and the frequency of treatment-related AEs/SAEs did not reveal any significant differences between the study arms ($P > 0.05$).

Table 13. Assessment of safety in the Phase II study (Arm 1: BCD-085 40 mg, Arm 2: BCD-085 80 mg, Arm 3: BCD-085 120 mg, Arm 4: placebo).

Abnormality	Arm			
	1 (n = 31)	2 (n = 30)	3 (n = 28)	4 (n = 28)
Any AEs/SAEs	14 (45.16%)	11 (36.67%)	7 (25.00%)	11 (39.29%)
P value[2]	0.443			
Treatment-related AEs/SAEs	6 (19.35%)	3 (10.00%)	2 (7.14%)	3 (10.71%)
P value[1]	0.534			
AEs, Grade 3	1 (3.23%)	1 (3.33%)	1 (3.47%)	2 (7.14%)
P value[1]	0.872			
Treatment-related AEs, grade 3	1 (3.23%)	1 (3.33%)	0	0
P value[1]	1.000			
Injection site reactions	1 (3.23%)	0	0	0
P value[1]	1.000			
Treatment discontinuation due to AEs/SAEs	None			
Any SAEs				
AEs, grade 4				
Note: [1] two-sided Fisher's exact test; [2] Pierson's χ^2 test with Yates correction.				

In this study, no grade 4 AEs and no SAEs were recorded. No patients had to discontinue the study treatment due to AEs/SAEs.

The most common AEs were neutropenia, acute respiratory tract infections, increased blood pressure, and elevated liver transaminases. Most of the AEs were mild in severity. Grade 3 AEs were reported in 3.23% of patients in Arm 1, 3.33% of patients in Arm 2, 3.57% patients in Arm 3, and 7.14% patients in Arm 4 (p=0.872, two-sided Fisher's exact test).

Only one injection site reaction (grade 1) was detected in Arm 1 manifesting as swelling in the injection site. The investigator did not consider this event clinically meaningful. The

frequency of this case was 3.23% of all patients in Arm 1 (P = 1.000, two-sided Fisher's exact test).

BCD-085 40 mg, 80 mg, and 120 mg demonstrated a favorable safety profile. The nature and severity of adverse events seen in three BCD-085 arms did not significantly differ from that in the placebo arm.

The immunogenicity assessment did not detect binding anti-BCD-085 antibodies in any patient.

The PK analysis demonstrated dose-dependent changes in the BCD-085 concentration over time. The serum concentration of BCD-085 increased gradually in a linear mode and reached its maximum by the end of Week 1. With re-administrations, BCD-085 accumulated in the serum, and its concentration increased [redacted] Higher doses (80 mg and 120 mg) showed higher induction potential as compared with 40 mg, because fewer injections were needed to achieve concentrations around $C_{max\text{-}mult.}$ This finding justified further investigation of a regimen with less frequent BCD-085 injections (once every 4 weeks).

Thus, the study showed that BCD-085 40 mg, 80 mg, and 120 mg was significantly superior to placebo in patients with moderate to severe plaque psoriasis. The best response was observed in the arm treated with 120 mg BCD-085.

1.3.2.2.2.2. Results of the extension period of the efficacy and safety study of BCD-085 in patients with psoriasis

The extension period of the Phase II study aiming to assess the efficacy and safety of multiple SC doses of BCD-085 80 mg and 120 mg in patients with moderate to severe plaque psoriasis who completed the BCD-085-2 study has been completed.

The study involved 103 adult patients with moderate to severe plaque psoriasis who completed the BCD-085-2 study. After the investigator decided to include the patient in the study, PASI and its relative improvement vs. baseline for the BCD-085-2 study were determined. According to the results, the patient was distributed into one of two study arms:

- 120 mg arm (< PASI 50 vs. baseline). During the first 12 weeks of the BCD-085-2ext study, patients of this arm received BCD-085 120 mg subcutaneously (three injections of 1.0 mL each) once every 2 weeks;

- 80 mg arm (≥ PASI 50 vs. baseline, patients with moderate and high response). During the first 12 weeks of the BCD-085-2ext study, patients of this arm received BCD-085 80 mg subcutaneously (two injections of 1.0 mL each) once every 2 weeks.

At Week 12 from the inclusion in the BCD-085-2ext study, all patients were assessed for PASI 100 response. PASI 100 responders received the same doses of BCD-085 once every 4 weeks at subsequent visits. PASI 100 non-responders received BCD-085 once every 2 weeks until the end of the study.

Thus, efficacy data were assessed in 4 arms:

- Arm 1: BCD-085 120 mg (once every 2 weeks / once every 4 weeks),
- Arm 2: BCD-085 80 mg (once every 2 weeks / once every 4 weeks),
- Arm 3: BCD-085 120 mg (once every 2 weeks),
- Arm 4: BCD-085 80 mg (once every 2 weeks).

The primary efficacy endpoint of this study was the proportion of patients who achieved PASI 75 by Week 38 of the extension study (or Week 52 if considering the participation in the main study BCD-085-2). The analysis showed that the proportion of patients who achieved PASI 75 after 1 year of treatment with BCD-085, in the ITT population (n=103), was 98.06% (including non-responders – patients who failed to achieve PASI 50 at the moment of inclusion in the extension phase). In the PP population (n=101), PASI 75 was achieved by 98.02% of patients.

In this study, there were two subpopulations: a subpopulation highly sensitive to the study treatment (Arms 1 and 2, where patients received BCD-085 once every 4 weeks, n = 45), and a subpopulation of patients who responded slower (Arms 3 and 4, where patients received BCD-085 once every 2 weeks throughout the entire study; n = 58).

Results of the PASI 75 assessment in the ITT population are presented below.

A comparison in the subpopulation of patients more sensitive to the therapy (Arms 1 and 2) showed the absence of significant differences ($P = 1.00$, two-sided exact Fisher's test) between BCD-085 80 mg and 120 mg. However, the efficacy was the highest with BCD-085 120 mg (Arm 1): PASI 75 was achieved by 100% of patients.

A comparison in the subpopulation of patients less sensitive to the therapy (Arms 3 and 4) also showed no significant differences. Arm 3 showed a lower response because it included the most severe patients, who did not have the minimal response (PASI 50) at the inclusion in the extension phase and failed to achieve PASI 100 after 12 weeks of the treatment. However, 95.24% of patients in this arm achieved PASI 75, which confirms the high efficacy of the therapy even in slow responders.

The loss of clinical response in patients receiving BCD-085 for 1 year was assessed. This was done by evaluating the proportion of patients with a loss of PASI 75/90/100 response at Week 38 (i.e. after 1 year of therapy) of the extension period vs. Week 12 of the BCD-085-2 study among patients receiving BCD-085 in both studies (n=77).

Overall, the results allow making a conclusion on the high efficacy of BCD-085 during long-term use: 98.06% of patients achieved meaningful clinical improvement in psoriasis regardless of the dose and dosing regimen of BCD-085. The highest efficacy was recorded in patients receiving BCD-085 120 mg Q2W until Week 12 and then switched to the Q4W regimen: by the end of the follow-up, 100% of these patients achieved PASI 100 (i.e. a 100% improvement in PASI score) and sPGA score 0-1.

In the population of patients receiving BCD-085 for 1 year (during the main study BCD-085-2 and the extension study BCD-085-2ext), PASI 75 was lost only in 2.6% of subjects. Cases of loss of PASI 90/100 response were seen more often in the arms receiving BCD-085 80

mg, thus showing that this dose was not effective enough. Among patients receiving BCD-085 120 mg during the last 6 months of the study treatment, neither subject lost PASI 100 despite less frequent dosing (once every 4 weeks).

Regardless of the dose and dosing regimen, BCD-085 showed a favorable safety profile, which did not differ between the arms. During the period studied, at least one AE/SAE was recorded in 36.89% of patients (38/103): in 33.33% of patients (2/6) in Arm 1; 35.90% of patients (14/39) in Arm 2; 38.10% (8/21) of patients in Arm 3; 37.84% (14/37) of patients in Arm 4 (P = 1.00, exact Fisher's test).

Table 16. Safety assessment in the extension period of Phase II study.

	All patients	Arm				*P* value[1]
		1 (n=6)	2 (n=39)	3 (n=21)	4 (n=37)	
Any AEs/SAEs	38 (36.89%)	2 (33.33%)	14 (35.90%)	8 (38.10%)	14 (37.84%)	1.00
Treatment-related AEs/SAEs	6 (5.83%)	0 (0%)	4 (10.26%)	1 (4.76%)	1 (2.70%)	0.6542
Any SAEs	1 (0.97%)	0 (0%)	1 (2.56%)	0 (0%)	0 (0%)	1.00
Treatment-related SAEs	None					-
AEs, grade 3/4	5 (4.85%)	1 (16.67%)	2 (5.13%)	0 (0%)	2 (5.41%)	0.3528
Treatment-related AEs, grade 3/4	5 (4.85%)	1 (16.67%)	2 (5.13%)	0 (0%)	2 (5.41%)	1.00
Injection site reactions	None					-
Treatment discontinuation due to AEs/SAEs						
Note: [1] two-sided exact Fisher's test, comparison of Arms 1 to 4						

Treatment-related AEs/SAEs were recorded in 5.83% of patients (6/103): four patients in Arm 2 (10.26%), one patient in Arm 3 (4.76%), and one patient in Arm 4 (4.70%) (p=0.6542, two-sided exact Fisher's test).

During the study, two SAEs not related to the study treatment were recorded in one patient of Arm 2 (2.56%). In both cases, hospitalization was a seriousness criterion. Grade 3/4 AEs not related to the study therapy were recorded in 4.85% of patients (5/103): one patient in Arm 1, two patients in Arms 2 and 4, and no patients in Arm 3.

The most common AEs were lymphocytosis, liver function tests increased, total bilirubin increased and blood pressure increased. The rest of AEs were reported in single cases. The AEs

were mostly mild to moderate in severity (grade 1/2, CTCAE 4.03). No cases of treatment discontinuation due to AEs or SAEs were recorded. No injection site reactions were recorded after use of BCD-085.

The immunogenicity analysis did not show binding anti-drug antibodies after 42 weeks of the BCD-085-2ext study (i.e. 56 weeks from the beginning of the BCD-085-2 study).

Thus, the overall analysis demonstrated high efficacy of long-term use of BCD-085 in patients with moderate to severe plaque psoriasis who failed to respond to previous standard therapy. The maintenance treatment period showed that BCD-085 can be used less often (once a month) if administered at a dose of 120 mg.

1.3.2.2.2.3. Results of the efficacy and safety study of BCD-085 in patients with ankylosing spondylitis

The second Phase II study ("An International, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-finding Clinical Study of the Efficacy and Safety of Repeated-dose Subcutaneous BCD-085 in Patients with Active Ankylosing Spondylitis") aimed at finding the optimal BCD-085 doses and treatment regimen for patients with active ankylosing spondylitis and at investigating the efficacy, safety, and pharmacokinetics of BCD-085 (BCD-085-3 study).

According to the approved Protocol, the study involved 88 adults with active ankylosing spondylitis. Before being included in the active phase of the study, all patients underwent a screening examination (max duration: 28 days) to determine whether they met the eligibility criteria. After the patient completed the screening procedures and the Investigator qualified the patient eligible for the study, the patient was stratified according to the baseline CRP level (normal/elevated), BASDAI score (4-6/≥ 7), prior exposure to TNF-alpha inhibitors or other therapeutic monoclonal antibodies for the treatment of AS (experienced/naive), and need for DMARD therapy (yes/no). Stratified patients were then randomized 1:1:1:1 to 4 study arms (Arm 1: BCD-085 40 mg, Arm 2: BCD-085 80 mg, Arm 3: BCD-085 120 mg, Arm 4: placebo).

Thus, in the active phase of the study, patients were given injections of the test drug/placebo weekly for the first three weeks of treatment and then once every 2 weeks until Week 12. After the active phase, there was a 4-week follow-up.

The **treatment efficacy** was assessed by finding the proportion of ASAS20 responders at Week 16 of the study. The final efficacy analysis included 87 patients (22 from each BCD-085 arm and 21 from the placebo arm).

In all BCD-085 arms, the proportion of ASAS20 responders at Week 16 was more than 70%, while in the placebo arm, only about 40% of patients responded to the treatment. Significant differences in the ASAS20 rate were seen between all the arms ($P < 0.05$, two-sided Fisher's exact test).

Table 17. Proportion of ASAS20 responders at Week 16, by study arms.

Arm	**Drug**	**Proportion of ASAS20 responders, n (%)**	***P* value**
1 (n=22)	BCD-085 (40 mg)	16 (72.73%)	**$P_1 = 0.0043$**
2 (n=22)	BCD-085 (80 mg)	18 (81.82%)	
3 (n=22)	BCD-085 (120 mg)	20 (90.91%)	
4 (n=21)	Placebo	9 (42.86%)	
Note: [1] two-sided Fisher's exact test.			

To prove the hypothesis of BCD-085 being superior to placebo, the 95% CIs were provided for the difference in the ASAS20 rate for each pairwise comparison (each of BCD-085 arms versus placebo). The lower bound of the derived 95% CI had to exceed the pre-specified margin (δ) of clinically non-meaningful differences set as 10% (0.10).

This table shows that the lower bounds of the 95% CIs for all pair-wise comparisons (placebo versus BCD-085) fall outside the pre-specified superiority margin (δ = 0.10) for 80 mg and 120 mg BCD-085. Thus, the hypothesis of BCD-085 80 mg and 120 mg being superior to placebo in patients with active ankylosing spondylitis was accepted, and the primary study endpoint was achieved.

The secondary endpoint analysis showed that the ASAS20/40 and ASAS 5/6 rates at each assessment visit were higher in the BCD-085 arms than in the placebo arm. However, the pair-wise comparisons found these differences to be significant not for all assessment points. The most pronounced and quick changes were seen in patients receiving BCD-085 120 mg. This arm showed a significant superiority to placebo in ASAS40 and ASAS5/6 rates at Weeks 12 and 16.

Similar results were obtained with other secondary endpoints. All assessed responses were higher in the BCD-085 arms than in the placebo arm, but the longest and fastest response was seen in the BCD-085 120 mg arm. In this arm, significant improvements in the BASDAI, ASDAS-CRP, BASMI, MASES, BASFI, CRP, and pain severity were seen as early as at the second assessment at Week 4 (for pain severity at Week 2). These improvements were maintained throughout the entire study, thus suggesting a significant decrease in the activity of ankylosing spondylitis.

Changes in other endpoints (chest expansion) were less pronounced. However, improvements were seen for all endpoints, and they were the greatest with BCD-085 120 mg.

BCD-085 was proved superior to placebo. The primary study goal was achieved. Comparison of additional efficacy measures at different timepoints showed that the most pronounced and fast response was achieved with BCD-085 120 mg.

The safety analysis included 88 patients who received at least one dose of BCD-085/placebo. BCD-085 (all tested dose levels) demonstrated a favorable safety profile with adverse events not differing in nature and severity from those seen with placebo.

At least one AE/SAE was recorded in 45.45% (10) of patients in the BCD-085 40 mg arm, 27.27% (6) of patients in BCD-085 80 mg arm, 18.18% (4) of patients in the BCD-085 120 mg arm and 31.82% (7) of patients in the placebo arm ($P = 0.298$, two-sided Fisher's exact test). The arms did not differ in the proportion of patients with treatment-related adverse events (22.73%, 18.18%, 4.55% and 22.73%, $P = 0.354$, two-sided exact Fisher's test).

The arms were also similar in the rates of severe AEs (grade 3/4), including those related to treatment ($P > 0.05$, two-sided Fisher's exact test)

There was only one dropout due to an AE. A patient from BCD-085 80 mg arm discontinued the study after Visit 6 due to the AE "erosive colitis" (CTCAE 4.03 grade 3), which was not related to the study therapy. No serious adverse events, injection site reactions or deaths were recorded.

Table 19. Safety assessment in the Phase II study in patients with active ankylosing spondylitis.

Abnormality	Arm				Value p
	BCD-085 40 mg (n = 22)	BCD-085 80 mg (n = 22)	BCD-085 120 mg (n = 22)	Placebo (n = 22)	
Any AEs/SAEs	10 (45.45%)	6 (27.27%)	4 (18.18%)	7 (31.82%)	0.298[1]
Any AEs	10 (45.45%)	6 (27.27%)	4 (18.18%)	7 (31.82%)	0.298[1]
Any SAEs	0	0	0	0	-
Treatment-related AE	5 (22.73%)	4 (18.18%)	1 (4.55%)	5 (22.73%)	0.354[1]
AEs, grade 3/4	1 (4.55%)	2 (9.09%)	0	1 (4.55%)	0.900[1]
Treatment-related AEs, grade 3/4	0	1 (4.55%)	0	1 (4.55%)	1.00[1]
Injection site reactions	0	0	0	0	-
Treatment discontinuation due to AEs/SAEs	0	1 (4.55%)	0	0	1.00[1]

Note: [1] two-sided Fisher's exact test.

The vast majority of adverse events were represented by single episodes throughout the entire study. The most common adverse events were infections and blood and lymphatic system disorders. Cardiovascular disorders were slightly less common. Most adverse events, including treatment-related ones, were mild to moderate (CTCAE 4.03 grade 1/2), thus suggesting a favorable safety profile of BCD-085. No statistically significant differences were revealed between the arms for any AE.

The immunogenicity assessment did not detect binding anti-BCD-085 antibodies in any patient.

Statistical analysis showed dose-dependent pharmacokinetics of BCD-085. The induction potential was similar for all test doses.

Thus, the study showed that the efficacy of BCD-085 80 mg and 120 mg was significantly superior to that of placebo in patients with active ankylosing spondylitis. The best response was observed in the arm treated with BCD-085 120 mg.

1.3.2.2.2.4. Results of the extension period of the efficacy and safety study of BCD-085 in patients with ankylosing spondylitis

The extension period of the Phase II study "An International, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-finding Clinical Study of Efficacy and Safety of Repeated-dose Subcutaneous BCD-085 in Patients with Active Ankylosing Spondylitis" aimed to compare the efficacy and safety of multiple subcutaneous doses of BCD-085 80 mg and 120 mg in patients with active ankylosing spondylitis who completed the BCD-085-3 study. BCD-085-3ext study ("An International, Multicenter, Open-label, Comparative Clinical Study of the Efficacy and Safety of Multiple Subcutaneous Doses of BCD-085 80 mg and 120 mg in Patients with Ankylosing Spondylitis Who Completed the BCD-085-3 Study").

The study involved 81 adult patients with ankylosing spondylitis who completed the previous study BCD-085-3. On the basis of ASAS20 response (vs. screening for BCD-085-3 study), the patients were distributed into two arms:

- Arm 1: patients who achieved ASAS20 by Week 16 of the BCD-085-3 study. In the extension study, they received BCD-085 80 mg subcutaneously (2.0 mL) once every 2 weeks through Week 36 (52).
- Arm 2: patients who failed to achieve ASAS20 by Week 16 of the BCD-085-3 study. In the extension study, they received BCD-085 120 mg subcutaneously once every 2 weeks through Week 36 (52).

More than 70% of patients achieved ASAS response (ASAS20/40, ASAS5/6) at each assessment point (Weeks 28, 40, 52) during the extension study regardless of the dose used.

Other endpoints in the total population (n=81) demonstrated similar trends: a statistically significant improvement achieved by the first assessment point of the extension study [Week 12 (28)], then a stable response that maintained without changes through the study end.

The analysis of the ASAS20/40 rate over time did not detect trends towards a loss of response during the extension study. By the end of the extension study, only 7.41% (4) of patients (ASAS20) and 10.26% (4) of patients (ASAS40) lost their response achieved after 16 weeks of the main study BCD-085-3.

The extension period showed that the long-term use of BCD-085 120 mg resulted in a pronounced clinical response in patients who failed to respond during the first 16 weeks of the

therapy. The proportions of ASAS20, ASAS40, and ASAS5/6 responders by the end of the extension period were 63.16%, 52.63%, and 52.63%, respectively.

Other secondary endpoints (BASDAI, ASDAS-CRP, BASMI, MASES, BASFI) showed similar changes over time: an improvement vs. Week 16 of the main study BCD-085-3 by the first assessment point in the extension study [Week 12 (28)] with a stable response through the end of the study. The data show that patients from Arm 1 (BCD-085 80 mg) had low levels of all main AS activity indexes at inclusion in the extension study (Week 16 of BCD-085-3 study). Continuation of the treatment with BCD-085 in these patients resulted in the stabilization of the achieved effects (mean values of most indexes achieved a plateau).

Patients from Arm 2 (120 mg) had baseline indexes higher than in the 80 mg arm (1.5-2-fold higher) because the 120 mg arm included patients who failed to achieve response at Week 16 of the main study. During further 36 weeks, BCD-085 120 mg resulted in statistically significant decreases in BASDAI, BASFI, BASMI, and pain scores.

The safety population included all patients who received at least one dose of BCD-085 during the extension study BCD-085-3ext (n=81).

At least one AE was recorded in 40.74% (33) of patients. Of those, the AEs were considered by the investigators to be related to the study treatment in 28.40% (23) of patients. No SAEs were recorded during the extension study (40 weeks).

During the BCD-085-3ext study, there were 2 cases of patients' withdrawal due to adverse events (microbial eczema, positive Diaskintest). No grade 4 adverse events and deaths were recorded in study subjects.

The vast majority of adverse events were represented by single episodes throughout the entire study. The most common adverse events were from two system organ classes: infections

and infestations and blood and lymphatic system disorders. Cardiovascular and hepatobiliary disorders were less common.

Most adverse events, including treatment-related ones, were mild to moderate (CTCAE 4.03 grade 1/2), thus suggesting a favorable safety profile of BCD-085. Four patients had severe grade 3 adverse events (neutropenia, GGT increased, ARVI and blood pressure increased). The vast majority of treatment-related adverse events were expected and mild to moderate.

Two cases of positive Diaskintest with normal chest X-ray were recorded during the study. It should be noted that no active tuberculosis infection was recorded in the study subjects with positive Diaskintest results during the study. Special attention should be paid to AE “esophagus candidiasis” recorded in one patient (1.23%). Candida infections of various localization, in particular, esophagus, have been described for interleukin-17 blockers. These events are classified as adverse events of special interest. In the extension study, esophagus candidiasis was of grade 2 and resolved without sequelae after a medication therapy.

If considering the route of administration (SC injections), injection site reactions are expected for BCD-085. The proportion of patients with injection site reactions was 1.23% (one patient had two local reactions, which included hyperemia, swelling, itch, pain and local infiltrate). This shows a low incidence rate of this AE.

To assess the risk of increasing AE/SAE rate during the long-term use of BCD-085, exposure-adjusted AEs incidence rate (EAIR) was assessed during the extension phase and compared with that during the BCD-085-3 study. The EAIR for the BCD-085-3 study was 1.379, for the BCD-085-3ext – 0.588. Thus, the frequency of AE/SAE showed a tendency towards a decrease during the long-term use, suggesting no risk of AE rate increase over time.

The immunogenicity assessment did not detect binding anti-BCD-085 antibodies in any patient.

Thus, the obtained data confirmed the high efficacy of BCD-085 (JSC BIOCAD, Russia) in ankylosing spondylitis. The response was stable over time; it was more frequent with BCD-085 120 mg. The safety profile of BCD-085 was favorable.

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 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 skin damage. Taking this information into account, 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 was confirmed in a number of clinical studies.

JSC BIOCAD has developed an original monoclonal anti-IL-17 antibody (BCD-085), which has several competitive advantages over other drugs of this class. BCD-085 has modified Fc regions and CDRs, [redacted] respectively.

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 and potency. A set of experiments in relevant animal species (cynomolgus monkeys) [redacted] demonstrated the pharmacodynamic effect of BCD-085, which is 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 of a large non-clinical program allowed for conducting a Phase I clinical study in healthy volunteers and Phase II studies in patients with moderate to severe plaque psoriasis and in patients with active ankylosing spondylitis. BCD-085 confirmed the previously discovered characteristics such as high efficacy and favorable safety profile. Pharmacokinetics of BCD-085 was typical for monoclonal antibodies. The drug was shown to have a long half-life period. The Phase II studies showed that upon repeated injections of BCD-085 40 mg, 80 mg, and 120 mg, the minimum serum concentration was rather high (> 60% C_{max}) and was reached before the second injection of BCD-085. With re-administrations, BCD-085 accumulated in the serum, and its concentration increased [redacted] Higher doses (80 mg and 120 mg) showed higher induction potential as compared with 40 mg because fewer injections were needed to achieve concentrations around $C_{max\text{-}mult}$. Thus, it was decided to assess a less frequent dosing regimen (once every 4 weeks after induction).

Thus, BCD-085 can be recommended for further clinical development in the target populations 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 IL-17 blockade. Investigating this drug 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. Summary of the known and potential risks and benefits, if any, to human subjects (risk/benefit balance)

1.4.1. Benefit assessment

BCD-085 is an innovative drug the toxicity, safety, and pharmacokinetics of which was investigated in animals, in the Phase I clinical study in healthy volunteers, and in the Phase II clinical studies in patients with moderate to severe plaque psoriasis and in patients with ankylosing spondylitis. 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. This clinical study aims at investigating the efficacy and safety of a less frequent dosing regimen of BCD-085 (once every 4 weeks) versus BCD-085 every 2 weeks and versus placebo in patients with moderate to severe plaque psoriasis. This means that some study subjects will be randomly assigned to the placebo arm during the first period of the study and, thus, may not get any personal benefit from being in the study other than getting a comprehensive medical examination. However, the information obtained after the study is completed will be of high scientific value and may help to implement in clinical practice a new effective treatment for autoimmune diseases. At the end of this period, all patients (including those from the placebo arm) will be switched to BCD-085, which should result in good treatment response. If the study achieves its primary endpoint, BCD-085 will be administered less frequently (and thus more conveniently for patients).

1.4.2. Risk assessment

BCD-085 is a new drug, so its effects in humans are not enough investigated. The pharmacodynamic effects of blocking human IL-17 suggest 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); during the study potential complications will

be carefully monitored. Thus, it is expected that the risk of infectious complications for the patients involved in the study will be minimal. Risk of allergic reactions cannot be ruled out in subjects with hypersensitivity to ingredients of BCD-085. The method of administration (subcutaneous injections) and protein nature of BCD-085 suggest that there is a risk of injection site reactions.

[redacted]

The 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) were rarely 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.

In one Phase II clinical study, SC injections of BCD-085 40 mg, 80 mg, and 120 mg in patients with moderate to severe plaque psoriasis were well tolerated; no serious adverse events or grade 4 adverse events were reported. Nobody withdrew from the study due to adverse events. The most common AEs were neutropenia, acute respiratory tract infections, increased blood pressure, and elevated liver transaminases. Most of the AEs were mild in severity. Only one injection site reaction (grade 1) was detected in Arm 1 manifesting as swelling in the injection site. The investigator did not consider this event clinically meaningful.

Another Phase II clinical study showed that BCD-085 at doses of 40 mg, 80 mg, and 120 mg has a favorable safety profile in patients with ankylosing spondylitis. The vast majority of adverse events were represented by single episodes throughout the entire study. The most common adverse events were infections and blood and lymphatic system disorders. Cardiovascular disorders were slightly less common. Most adverse events, including treatment-related ones, were mild or moderate in severity (CTCAE 4.03 grade 1/2). Grade 3/4 AEs were registered as single episodes in all arms including the placebo arm. Thus, the safety profile of BCD-085 was considered favorable. No SAEs were reported in this study. The immunogenicity assessment did not detect binding anti-BCD-085 antibodies in any patient.

1.4.3. Conclusions

Findings from physicochemical investigation, non-clinical development, the clinical study of PK, safety, and tolerability in healthy volunteers, the clinical studies of the efficacy and safety of multiple SC injections of different doses of BCD-085 in patients with moderate to severe plaque psoriasis and in patients with ankylosing spondylitis provided 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 development program, including that in patients with psoriasis, will have a positive effect with low risk of adverse reactions. Thus, the overall risk/benefit ratio for BCD-085 is considered favorable for the patients.

1.5. Description of and justification for the route of administration, dosage, dosing regimen, and treatment period

1.5.1 Description and justification of the study design

This is an international multicenter double-blind randomized study to compare the efficacy and safety of two dosing regimens of BCD-085 (JSC BIOCAD, Russia) in patients with moderate to severe plaque psoriasis in 3 parallel arms [Arm 1: BCD-085 120 mg Q2W after induction; Arm 2: BCD-085 Q4W after induction; Arm 3: placebo (until Week 10), blinded therapy]. At Week 12, the therapy will be unblinded, and the efficacy will be assessed. Starting from Week 14, patients in Arm 1 will receive BCD-085 Q4W through Week 50. Starting from Week 14, patients in Arm 2 will continue to receive BCD-085 Q4W through Week 50. Patients from Arm 3 will receive BCD-085 at Weeks 12, 13 and 14, then Q4W (from Week 18 through Week 50). To assess long-term efficacy and safety of BCD-085, and to evaluate maintenance of the stable treatment effect with no increased safety risk after 1-year treatment, the treatment in ≥PASI 75 responders at Week 52 will be continued Q4W starting from Week 54 through Week 154 (in patients from Arms 1 and 2) or through Week 166 (in patients from Arm 3).

Since the planned population size is 213 patients with moderate to severe plaque psoriasis, it is unlikely that all of them can be recruited at one study site. To ensure optimal timing, patients will be recruited at several sites.

In this study, the effects of BCD-085 will be compared with the effects of placebo to make adequate and objective conclusions on the efficacy and safety of BCD-085. The necessity of using 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 minimize 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.

Patients in all three arms will receive the treatment in parallel. This is important to obtain objective results and eliminate the possibility of external factors to affect treatment efficacy and safety. It is known, for example, that psoriasis patients commonly have seasonal exacerbations, and by using the parallel-group design, the effect of the season on the study results will be eliminated.

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

This Phase III study aims to evaluate the efficacy and safety of BCD-085 Q4W vs. BCD-085 Q2W vs. placebo in patients with moderate to severe plaque psoriasis and to investigate long-term efficacy and safety of BCD-085 in this population. In drug development, treatment duration should be enough to establish the efficacy and safety of the drug but should not be too long because some patients are on placebo. 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]. It was decided to use a less frequent dosing regimen on the basis of the assessment of multiple-dose PK in the Phase II study. It showed that with repeated administrations BCD-085 accumulated in serum, and its concentrations increased several times. Thus, BCD-085 can be used less frequently after the induction period.

The primary endpoint in 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 PASI 75 responders is widely used in clinical development to evaluate the efficacy of psoriasis drugs and is also 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 was used in Phase III 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 static Physician's Global Assessment (sPGA), Nail Psoriasis Severity Index (NAPSI), 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]. NAPSI was used in several Phase 3 studies of ixekizumab (an anti-IL-17 antibody) (RHAZ, RHBA studies[18]). It significantly improved in patients with psoriatic nail involvement.

[18] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003943/WC500205806.pdf

The recent findings suggest that interleukin-17 plays a key role in the development of psoriasis. Clinical studies of drugs blocking the IL-17 signaling (ixekizumab, brodalumab, and secukinumab) demonstrated high efficacy of this approach in the treatment of patients with moderate to severe plaque psoriasis with the PASI 75 response seen in 70% to 80% of patients as early as after 12 weeks of treatment [15-21]. Thus, moderate to severe plaque psoriasis is considered a model sensitive enough for clinical investigation of BCD-085.

1.5.2. Description of and justification for the route of administration, dosage, dosing regimen, and treatment period

In **Arm 1**, the test drug BCD-085 will be used at a dose of 120 mg given as two subcutaneous injections according to the following schedule: once a week for the first 3 weeks (induction treatment), then Q2W through Week 10. After that, since Week 14, patients will receive BCD-085 Q4W through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 154.

In **Arm 2**, the test drug BCD-085 will be used at a dose of 120 mg given as two subcutaneous injections according to the following schedule: once a week for the first 3 weeks (induction treatment) and then Q4W (maintenance treatment) through Week 10. Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction therapy), Day 1 of Week 6, Day 1 of Week 10. To maintain the study blind, patients of this arm will receive placebo (2 injections) on Day 1 of Week 4 and Week 8. Starting from Week 14, patients will receive BCD-085 Q4W through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 154.

In **Arm 3** (control arm), patients will receive 2 subcutaneous injections of placebo (1.0 mL each) on Day 1 of Weeks 0, 1, 2, 4, 6, 8 and 10. Patients will receive BCD-085 120 mg once a week at Weeks 12, 13, 14, then Q4W starting from Week 18 through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 166.

Patients will be followed up for 4 weeks after the last injection of the investigational product.

BCD-085 is a potential therapeutic candidate for the long-term management of psoriasis. In the Phase II clinical study of the efficacy and safety of different doses of BCD-085, the drug was used as SC injections for better convenience of the patients because 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, and immunogenicity of BCD-085 in patients with the same route of administration that is planned to be implemented in routine clinical practice.

[redacted]

The main PK parameters of BCD-085 were characterized in the Phase I study. This study 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 studies”).

It was shown that doses closest to those planned to be used in the Phase II study were given to patients from Cohorts 4-6 (with account for patients’ body weight). Thus, it was considered that BCD-085 40 mg, 80 mg, and 120 mg will have pharmacokinetics similar to that seen in Cohorts 4-6 with the half-life ranging from 16 to 18 days. Thus, the Phase I of the clinical development allowed suggesting that BCD-085 should be used once every 2 weeks.

However, the PK study in the Phase II of the clinical development in patients with psoriasis showed that with re-administrations, BCD-085 accumulated in the serum, and its concentration increased [redacted] Higher doses (80 mg and 120 mg) showed higher induction potential as compared with 40 mg because fewer injections were needed to achieve concentrations around $C_{max\text{-}mult}$. Thus, it was decided to assess a less frequent dosing regimen (once every 4 weeks after induction). Less frequent dosing with the same treatment efficacy will allow a more comfortable and safe dosing regimen for the patients. At baseline, patients have acute inflammation that has to be resolved as soon as possible. This requires induction (higher) doses or an induction phase (more frequent injections). Clinical studies of the drugs inhibiting the signaling of interleukin-17 utilized both the first [16] and the second [17, 18, 20, 21] approaches. In this study, patients will receive

BCD-085 once weekly for 3 weeks for induction treatment. After that, patients will be switched to maintenance doses of BCD-085 (Arm 1: Q2W, after 10 weeks – Q4W; Arm 2: Q4W after induction). Patients of Arm 3 will receive BCD-085 at Weeks 12, 13, and 14, then Q4W (Week 18 through Week 50). To assess long-term efficacy and safety of BCD-085, and to evaluate maintenance of the stable treatment effect with no increased safety risk after 1-year treatment, the treatment in ≥PASI 75 responders at Week 52 will be continued Q4W starting from Week 54 through Week 154 (in patients from Arms 1 and 2) or through Week 166 (in patients from Arm 3).

Thus, the 120 mg dose, dosing frequency, and route of administration to be used in this study were chosen on the basis of the findings from non-clinical and phase I and II clinical studies of BCD-085 and available information on other anti-IL-17 monoclonal antibodies. Convenience for patients was also taken into account.

1.5.3. Justification of placebo use

Some of the patients 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 [15-22]. The necessity of using placebo in this case 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 not be exposed to excessive risk because of getting a placebo. If the disease worsens and requires additional therapy, the patient can always discontinue the study and receive all the medications he/she needs.

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 regulatory requirements

The clinical study will be conducted according to this Protocol developed in full compliance with the current law of the Russian Federation, Federal Law No. 61-FZ of April 12, 2010: *On the Circulation of Medicines*; National Standard of the Russian Federation GOST R 52379-2005 *Good Clinical Practice*; the rules of Good Clinical Practice of the Eurasian Economic Union; the Constitution of the Russian Federation; Federal Law No. 323-FZ of November 21, 2011: *On*

Public Health Protection in the Russian Federation; the WMA Declaration of Helsinki (Fortaleza 2013), Order No. 200n of April 01, 2016 *On Approval of the Good Clinical Practice*; the GCP principles, and the current law and regulations of the participating countries.

1.7. Description of study population

Men and women aged from 18 years (inclusive) and older with a confirmed diagnosis of moderate to severe plaque psoriasis (lasting for at least 6 months before signing the ICF) who did not respond to/are candidates for systemic therapy including TNF-α inhibitors or UV therapy.

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2. STUDY AIMS AND OBJECTIVES

2.1 Study aims

Study aim: To evaluate the efficacy and safety of BCD-085 Q4W vs. BCD-085 Q2W (standard dosing regimen) vs. placebo.

2.2 Study objectives

Objectives of the main study period

1. To compare the efficacy of BCD-085 in two dosing regimens and placebo using PASI 75 rate, sPGA score, and other secondary efficacy measures after 12 weeks of the treatment.
2. To compare the efficacy of BCD-085 in two dosing regimens and placebo using PASI 75 rate, sPGA score, and other secondary efficacy measures after 52 weeks of the treatment.
3. To evaluate the proportion of patients in each study arm who developed adverse events with repeated administration of BCD-085 or placebo. To compare the safety profiles of BCD-085 Q4W and BCD-085 Q2W.
4. To assess the immunogenicity of BCD-085 defined as the proportion of patients who developed anti-drug antibodies (binding/neutralizing).

Objectives of the extension study period

1. To assess maintenance of response during the long-term treatment with BCD-085 (for up to 154 weeks) and evaluate the safety profile of such treatment.
2. To assess the immunogenicity of BCD-085 defined as the proportion of patients who developed anti-drug antibodies (binding/neutralizing).

3. STUDY HYPOTHESIS

Two independent hypotheses will be tested during the study:

1. BCD-085 Q4W is not less effective than BCD-085 Q2W;
2. The efficacy of BCD-085 in both regimens is superior to placebo.

4. STUDY DESIGN

4.1. Primary and secondary outcome measures to be assessed in the study

4.1.1. Primary endpoint

- Proportion of patients who achieved PASI 75 at Week 12, by study arms.

4.1.2 Secondary endpoints

Efficacy endpoints during the main study period (Week 0 through Week 54):

- Proportion of patients who achieved PASI 75/90/100 at Weeks 8, 16, 24, 42 and 52, by study arms.
- Proportion of patients with sPGA score 0 or 1 at Weeks 8, 12, 16, 24, 42, and 52.
- Proportion of patients with sPGA score 0 at Weeks 16, 24, 42, and 52.
- Relative change from baseline in PASI score at Weeks 8, 12, 16, 24, 42 and 52.
- Change from baseline in itch severity measured with visual analog scale (0 mm to 100 mm) at Weeks 1, 12, 24, and 52.
- Change from baseline in Nail Psoriasis Severity Index (NAPSI) score at Week 12, 24, and 52.
- Change from baseline in Dermatology Life Quality Index (DQLI) score at Weeks 8, 12, 24, 42, and 52.
- Proportion of patients with DLQI score 0 or 1 at Weeks 24, 42, and 52.
- Proportion of patients (among those with psoriatic arthritis) who achieved an ACR20/50/70 at Weeks 12, 24, and 52.

Efficacy endpoints during the extension study period (Week 54 through Week 166)

- Proportion of patients who maintained PASI 75/90/100 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Proportion of patients who maintained sPGA 0-1 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.

- Proportion of patients who maintained sPGA score 0 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Proportion of patients who maintained DLQI score 0-1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Time to loss of PASI 75/90/100, sPGA 0-1/sPGA 0, DLQI 0-1 response during the treatment with BCD-085.
- Proportion of patients who maintained ACR 20/50/70 response (among patients with psoriatic arthritis) after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Proportion of patients who achieved PASI 75/90/100 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Proportion of patients with sPGA score 0 or 1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of the treatment with BCD-085.
- Proportion of patients who achieved sPGA score 0 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Change from baseline in itch severity measured with visual analog scale (0 mm to 100 mm) after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Change from baseline in Nail Psoriasis Severity Index (NAPSI) score after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085 (among patients with nail psoriasis at baseline).
- Proportion of patients who achieved DLQI score 0 or 1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Change from baseline in Dermatology Life Quality Index (DQLI) score after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.

Safety endpoints:

- Proportion of patients who developed AEs/SAEs.
- Proportion of patients who developed injection site reactions.
- Proportion of patients who developed Grade 3/4 AEs/SAEs.

- Proportion of patients who discontinued the study due to AEs and/or SAEs.
- Exposure adjusted incidence rate of AEs/SAEs during the extension study.

Immunogenicity endpoints

- Proportion of patients with anti-drug antibodies (binding/neutralizing).

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

Study design

The BCD-085-7 study is an international multicenter, randomized, double-blind, placebo-controlled clinical study comparing the efficacy and safety of two dosing regimens of BCD-085 (JSC BIOCAD, Russia) in patients with moderate to severe plaque psoriasis.

Before being screened for the study, patients must read and sign the informed consent form and undergo a screening examination (within 28 calendar days) to confirm that they are eligible for the study. The Protocol does not provide any additional requirements regarding the diet or physical activity during the screening or study period. The study is planned to enroll 213 adult patients with moderate to severe plaque psoriasis (diagnosed at least 6 months before signing the informed consent form) who have BSA ≥ 10%, PASI score ≥ 10, [19]and sPGA score ≥ 3.

Stratification and randomization

When the Investigator has decided that the patient can take part in the study, the patient should be stratified according to his/her body weight (<100 kg/≥100 kg), previous use of monoclonal antibodies for the treatment of psoriasis (previously treated/naive), PASI score (<20/≥20), and psoriatic arthritis (yes/no) and randomly assigned at a 2:2:1 ratio to one of the three study groups: 1) BCD-085 Q2W (Arm 1), 2) BCD-085 Q4W (Arm 2), 3) placebo (Arm 3).

Study periods

1. Screening (up to 28 days from signing the Patient Information Sheet with the Informed Consent Form, inclusive);
2. Main treatment period (from Week 0 through Week 54

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

3. Extension treatment period (from Week 54 through Week 154 in Arms 1 and 2, from Week 54 through Week 166 in Arm 3);
4. Follow-up period (from Week 154 through Week 158 in Arms 1 and 2, from Week 166 through Week 170 in Arm 3).

Screening period:

Up to 28 days from signing the Patient Information Sheet with the Informed Consent Form, inclusive.

Main study period (Week 0 to Week 54)

In this study period patients will be distributed to three arms:

- **Arm 1:** Patients in this arm (85 subjects) will receive BCD-085 120 mg (two subcutaneous injections, 60 mg in 1.0 mL each) once a week during the first 3 weeks (induction) and then once every 2 weeks through Week 10. Thus, the investigational product will be administered on Day 1 of Week 0, Week 1, Week 2, Week 4, Week 6, Week 8, and Week 10.
- **Arm 2:** Patients in this arm (85 subjects) will receive BCD-085 120 mg (two subcutaneous injections, 60 mg in 1.0 mL each) once a week during the first 3 weeks (induction) and then once every 4 weeks through Week 10. Thus, the investigational product will be administered on Day 1 of Week 0, Week 1, Week 2, Week 6 and Week 10. To maintain the study blind, patients of this arm will receive placebo (2 injections) on Day 1 of Week 4 and Week 8.
- **Arm 3:** Patients of this arm (43 subjects) will receive placebo (2 subcutaneous injections of placebo, 1.0 mL each) on Day 1 of Week 0, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10.

On Week 12, the treatment efficacy will be assessed with a PASI 75 score, and the treatment will be **unblinded**. Patients from Arms 1 and 2 will be given BCD-085 once every 4 weeks. Patients from Arm 3 will receive BCD-085 as follows:

- ✓ Induction: Weeks 12, 13, and 14, once a week;
- ✓ Weeks 18 through 50: once every 4 weeks.

Therefore, there will be 3 arms even after unblinding, and patients will receive BCD-085 according to the regimens described below:

a) Patients in Arm 1 will receive BCD-085 120 mg (2 SC injections of 60 mg each) once every 4 weeks starting from Week 14 and through Week 50.
b) Patients in Arm 2 will receive BCD-085 120 mg (2 SC injections of 60 mg each) once every 4 weeks starting from Week 14 and through Week 50.
c) Patients in this arm will receive BCD-085 120 mg once a week at Weeks 12, 13, 14, then once every 4 weeks through Week 50.

Unblinding will be performed at Visit 8 (Week 12) by opening the randomization envelops provided by the Sponsor with the investigational products.

Extension study period (from Week 54 through Week 154 for Arms 1 and 2, through Week 166 for Arm 3):

During **the extension study period (Week 54 to Week 166)** all patients who achieved PASI 75 at Week 52 will receive BCD-085 120 mg once every 4 weeks:

a) Patients from Arm 1 will receive BCD-085 from Week 54 through Week 154.
b) Patients from Arm 2 will receive BCD-085 from Week 54 through Week 154.
c) Patients from Arm 3 will receive BCD-085 from Week 54 through Week 166.

Patients who fail to achieve PASI 75 at Week 52 will be withdrawn from the study.

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

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

Patients who discontinue the study will not be replaced.

For further details see Section 11.6. *Study termination*.

In Arm 3, treatment will be extended by 12 weeks so that the total treatment duration in all arms can be 154 weeks. During the main treatment period (during the first 12 weeks of the study), patients from Arm 3 receive placebo, so the treatment period for these patients is extended to 166 weeks.

Regardless of the arm where the patient is assigned to, during the main study period (Week 0 through Week 54) SC injections will be performed by an authorized member of the study team at the study site (except for the injection on Week 54).

At Week 54 patients will be trained on how to self-inject the investigational product. If necessary, the training can be repeated at any of the subsequent visits.

During the extension study period (Week 54 to Week 154 for patients from Arms 1 and 2, Week 54 to Week 166 for patients from Arm 3), patients will self-inject the investigational product at home (on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150 in Arms 1 and 2; on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150, 158, 162 in Arm 3) after relevant training at the study site at Week 54. Injections of the investigational product on visit dates will be performed by an authorized member of the study team at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154 (in Arms 1 and 2) or at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154, 166 (in Arm 3). The first self-injection of the investigational product at Week 54 will be performed under the supervision of an authorized member of the study team.

Frequency of visits during the extension study period will be the following:

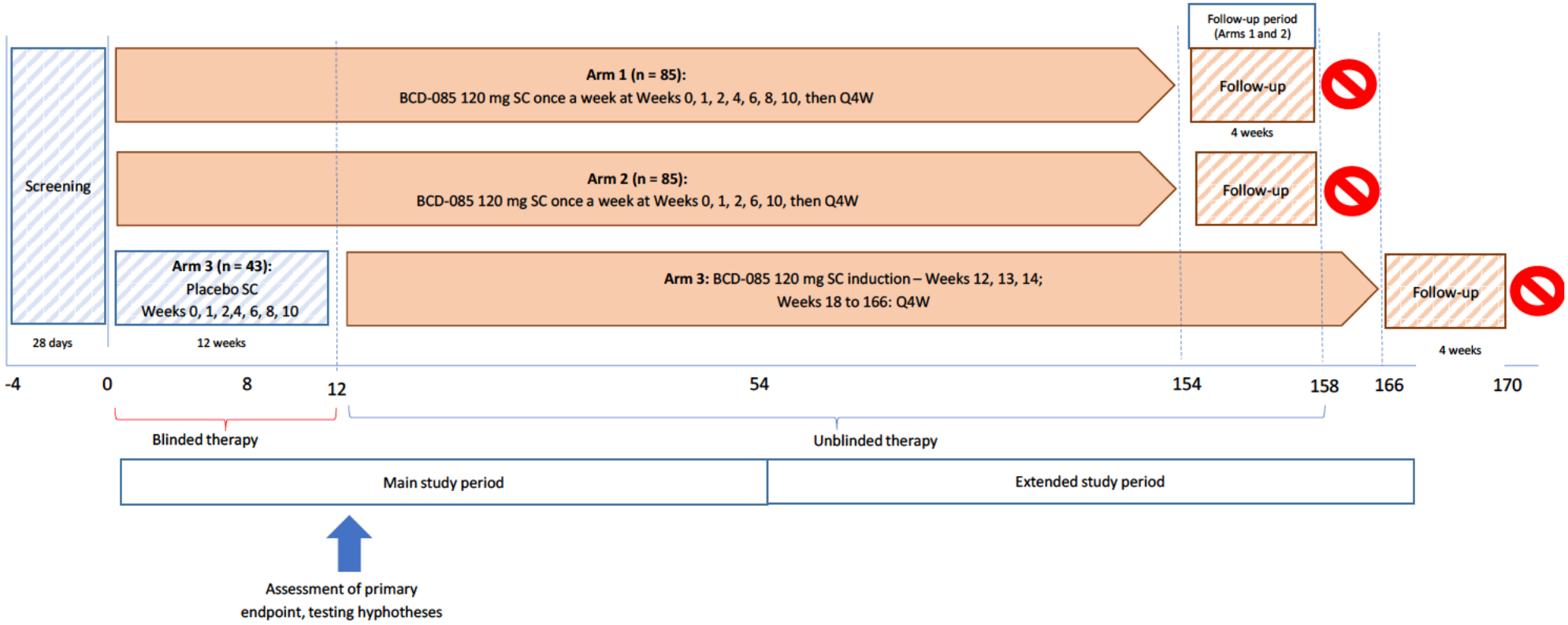
- For patients of Arms 1 and 2: once every 8 weeks (from Week 54 through Week 62), then once every 12 weeks (from Week 62 through Week 146), with the last treatment visit at Week 154.
- For patients of Arm 3: once every 8 weeks (from Week 54 through Week 62), once every 2 weeks (from Week 62 through Week 64), once every 10 weeks (from Week 64 through Week 74), once every 12 weeks (from Week 74 through Week 146), once every 8 weeks (from Week 146 through Week 154), with the last treatment visit at Week 166.

At each of the visits from Week 54 to Week 146 (for Arms 1 and 2) or to Week 154 (for Arm 3), BCD-085 will be dispensed to patients for self-administration at home at an amount sufficient until the next visit.

Follow-up period (4 weeks)

Patients will be followed up for 4 weeks after the last injection (Week 154 to Week 158 for Arms 1 and 2, Week 166 to Week 170 for Arm 3).

Figure 5. Study flow-chart



Treatment by study arms

In **Arm 1**, the test drug BCD-085 will be used at a dose of 120 mg given as two subcutaneous injections according to the following schedule: once a week for the first 3 weeks (induction treatment) and then once every 2 weeks through Week 10 (inclusive). After 10 weeks, patients will receive BCD-085 once every 4 weeks starting from Week 14 through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 154.

In **Arm 2**, the test drug BCD-085 will be used at a dose of 120 mg given as two subcutaneous injections according to the following schedule: once a week for the first 3 weeks (induction treatment) and then Q4W (maintenance treatment) through Week 10. Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction therapy), Day 1 of Week 6, Day 1 of Week 10. To maintain the study blind, patients of this arm will receive placebo (2 injections) on Day 1 of Week 4 and Week 8. After 10 weeks, patients will receive BCD-085 once every 4 weeks starting from Week 14 through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 154.

In **Arm 3** (control arm), patients will receive 2 subcutaneous injections of placebo (1.0 mL each) on Day 1 of Weeks 0, 1, 2, 4, 6, 8 and 10. Patients will receive BCD-085 120 mg once a week at Weeks 12, 13, 14, then Q4W starting from Week 18 through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 166. If failing to achieve ≥ PASI 75 response at Week 52, patients will discontinue the study.

Patients will be followed up for 4 weeks after the last injection of the investigational product.

Injections can be given to the abdomen, hips, or upper arms. Injections should be given at least 5 cm apart.

During the entire study, patients are not allowed to use phototherapy, systemic therapy or live vaccines.

Patients may use topical glucocorticoids (of mild to moderate potency) on the face, underarm, and genitals Patients may also use topical moisturizers, emollients, oils, and salicylic acid ointments, topical antibacterial and/or antimycotic agents as needed. 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 is 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 examination including:

- Baseline clinical characteristics and medical history,
- Physical examination,
- Blood pressure and wrist pulse,
- Electrocardiography,
- Chest[20] X-ray,
- Complete blood count,
- Blood chemistry,
- hs-CRP, atherogenicity index, apoB1/apoA1,
- Glycated hemoglobin HbA1C (only for patients with confirmed diabetes mellitus),
- Pregnancy test[21],
- Assessment of the patient's infection status [Diaskintest® or blood testing for TB (QuantiFERON or T-spot)]; examination by the TB Specialist (required if the Diaskintest®/QuantiFERON/T-spot test results are uncertain), anti-HIV antibodies and p24 antigen [HIVAg/Ab Combo], HBs-antigen, anti-HBcor antibodies [IgG + IgM/ IgM], and anti-HCV antibodies, qualitative PCR for HCV RNA/HBV DNA (only if the patient tests positive for respective antibodies), consultation with the Infectious Disease Specialist (required only if the patient tests positive for anti-HBcor or anti-HCV antibodies), microprecipitation reaction, and a direct hemagglutination assay (*T. pallidum*),
- Beck's depression inventory,

[20] Chest X-ray is performed according to the standards of the study site.
[21] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- Psoriasis area and severity (PASI), including body surface area affected by psoriasis (BSA), assessment of the nail psoriasis using NAPSI,
- Static Physicians Global Assessment (sPGA),
- Assessment of psoriatic arthritis (the 66/68 swollen/tender joint count), functional activity (HAQ-DI), disease activity (assessed by the physician and by the patient, VAS), patient assessment of pain (VAS), and markers of inflammation (C-reactive protein and ESR),
- Itch severity (VAS),
- DLQI questionnaire.

To measure the efficacy of treatment in the timeframes specified by the Protocol, changes over time in the PASI, NAPSI, and sPGA scores, VAS scores for itch severity, assessment of psoriatic arthritis (ACR 20/50/70), and quality of life (DLQI score) will be evaluated. [redacted]

For safety evaluation, the following will be closely monitored: all general disorders (including fever and flu-like syndrome), abnormal vital signs (blood pressure and wrist pulse), infectious complications, abnormal laboratory values (CBC results: hemoglobin, erythrocytes, platelets, leukocytes including changes in the leukocyte differential, ESR; blood chemistry: glucose, total bilirubin, ALT, AST, total protein, creatinine; urinalysis), assessment of cardiovascular risks (hs-CRP, atherogenicity index, apoB1/apoA1 ratio), cardiac disorders (ECG), lung disorders (chest X-ray). In some cases, to rule out tuberculosis or neoplasms that emerged during the study treatment, chest computed tomography can be done at the discretion of the TB Specialist.

For immunogenicity assessment, blood samples will be drawn from the patients and analyzed for binding and neutralizing anti-BCD-085 antibodies.

[redacted]

[redacted]

4.3. Measures to minimize/eliminate bias

4.3.1. Distribution of patients by study sites

Patients' recruitment at the study sites will be performed on a competitive basis. Recruitment can be re-opened if the Sponsor's audit reveals patients who do not meet the eligibility criteria or patients with major Protocol violations (with no explanation timely provided to the Sponsor).

4.3.2. Procedure of assigning study IDs

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

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

After signing the informed consent form, each patient receives a 5-digit screening ID consisting of a 2-digit site ID and a 3-digit subject's ID (continuing numbering in sequence, as patients are enrolled at this site). This information is recorded in the source documents and screening log. For example, in the study site 02, the first patient who has signed the informed consent form will receive the screening ID 02-001.

When all screening procedures are completed, and the investigator decides that the patient meets all the eligibility criteria, the investigator fills out a screening form and/or an eCRF and sends it to the BIOCAD's clinical study project manager via e-mail or fax: +7 (495) 992 82 98 (ext. 116). If JSC BIOCAD confirms the inclusion of this patient, a BIOCAD's representative stratifies and randomizes the patient, assigns him/her a Subject ID, and e-mails a Randomization Form (with the Subject ID and the drug lot number to be used in this patient) to the investigator. The investigator must record the subject's ID and lot in the source documents and the CRF.

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

"01" is the site ID,

"112" is sequential subject's ID in the study.

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

4.3.3. Stratification procedure

In order to make the arms as balanced as possible, patients will be first stratified, and then randomized.

Stratification will be performed by the following:

- Body weight (< 100 kg/100 kg and more),
- Prior experience with monoclonal antibodies for the treatment of psoriasis (MAb-experienced/MAb-naive),
- PASI score (> 20/≥ 20),
- Psoriatic arthritis (yes/no).

Table 21. Description of individual strata.

Stratum	Parameters
Stratum 1	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: no
Stratum 2	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 3	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no

Stratum	Parameters
Stratum 4	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: yes
Stratum 5	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: no
Stratum 6	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 7	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no
Stratum 8	• Body weight below 100 kg • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: yes
Stratum 9	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: no
Stratum 10	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 11	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no
Stratum 12	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI ≥ 20

Stratum	Parameters
	• Psoriatic arthritis: yes
Stratum 13	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: no
Stratum 14	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 15	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no
Stratum 16	• Body weight below 100 kg • The patient has received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: yes
Stratum 17	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: no
Stratum 18	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 19	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no
Stratum 20	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: yes
Stratum 21	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before

Stratum	Parameters
	• PASI < 20 • Psoriatic arthritis: no
Stratum 22	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 23	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no
Stratum 24	• Body weight of 100 kg or more • The patient has never received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: yes
Stratum 25	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: no
Stratum 26	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 27	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no
Stratum 28	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: yes
Stratum 29	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: no

Stratum	Parameters
Stratum 30	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI < 20 • Psoriatic arthritis: yes
Stratum 31	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: no
Stratum 32	• Body weight of 100 kg or more • The patient has received monoclonal antibodies before • PASI ≥ 20 • Psoriatic arthritis: yes

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

4.3.4. Randomization procedure

Randomization in the study will be centralized. Patients will be randomly assigned to three arms at a 2:2:1 ratio.

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 18 (1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18). Each number (1 to 18) corresponds to one of 18 possible unique blocks (see the table below). 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 between the arms. Therefore, each stratum will contain its own block sequence (symbols “1”, “2”, and “3” corresponding to the 2:2:1 distribution).

Table 22. Examples of blocks for block randomization.

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

Block	Principle of assigning to treatment arms
# 15	3,1,2,1,2
#16	3,2,1,1,2
#17	3,2,1,2,1
# 18	3,2,2,1,1

These blocks consist of the following symbols: “1”, “2” and “3”, and each of them corresponds to the study arms, for example, “1” to Arm 1, “2” to Arm 2, “3” to Arm 3.

Finally, a table is generated containing a random block sequence. Each stratum is assigned an infinite random sequence of blocks (an example is shown in 23).

Table 23. An example of assigning strata with block sequence.

Stratum	**Sequence of blocks**
Stratum 1	#1
	6
	5
	2
	…
Stratum 2	4
	3
	5
	#1
	…
Stratum 3	5

Stratum	Sequence of blocks
	5
	#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 patient'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 distributed 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 distributed to Arm 1 (e.g. the arm treated with BCD-085). After that, the patient is assigned a corresponding 3-digit randomization code (sequential number of the patient in the study), for example, "001" for the first patient, "002" for the second patient, etc. The investigator is notified about the Subject ID (consisting of the site ID and the sequential subject's ID in the study – "02-001") and the lot number of the investigational product that the subject is to receive.

Investigators can also 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 subject ID and the individual drug lot number are generated automatically. All numbers were automatically generated by the system after the Investigator enters all the required information.

The investigator must record the Subject ID and lot No in the source documents and the eCRF.

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

A representative of JSC BIOCAD will monitor the total number of enrolled patients. It is assumed that many patients would fail the screening since the eligibility criteria are rather strict. Therefore, the number of screened patients can be increased depending on the percentage of screening failures.

4.3.5. Blinding and subject-specific lots of investigational products

In the first, blinded, period of the study (until Week 12), neither investigators nor patients will know whether the active drug (BCD-085) or placebo is used.

The investigator (the principal investigator, a member of the study team responsible for the treatment of this patient) will receive BCD-085/placebo in identical secondary packaging (cartons). Each product will have an individual lot number. Each lot number is patient-specific.

Once the patient is enrolled in the study (randomized), the Sponsor will send to the investigator the Subject ID and appropriate lot number of the drug to be given to this patient. If the electronic randomization system is used, all numbers are generated automatically after the investigator enters all the required information. The investigator records the lot numbers in the source documents and the eCRF.

Starting from Week 12 treatment arms will be unblinded. The investigators and patients will be made aware of the drug and the dose used. There will be no individual lots during this study stage. Batch number should be recorded. Unblinding will be performed at Visit 8 (Week 12) by opening the randomization envelops provided by the Sponsor with the investigational products.

4.4. Description of the study treatment, doses, and dosing regimen of the investigational products. Description of the dosage form, packaging, and labeling of the investigational products

4.4.1. Description of the study treatment, doses, and dosing regimen of the investigational products

Patients in Arm 1 will receive BCD-085 120 mg given as two SC injections on Day 1 of Week 0, Week 1, Week 2, Week 4, Week 6, Week 8, Week 10 (blinded treatment period), then on Day 1 of Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50. If achieving ≥PASI 75 response at Week 52, patients will continue to receive BCD-085 120 mg once every 4 weeks starting from Week 54

(with injections given at Weeks 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 122, 126, 130, 134, 138, 142, 146, 150, 154).

In Arm 2, patients will receive BCD-085 120 mg as two SC injections on Day 1 of Weeks 0, 1, 2, 6, 10 (blinded treatment period). To maintain the study blind, patients of this arm will receive placebo (2 injections) on Day 1 of Week 4 and Week 8. At Week 12, treatment will be unblinded, and since then patients will continue to receive BCD-085 120 mg once every 4 weeks starting from Week 14. Thus, injections will be given at Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50. If achieving ≥PASI 75 response at Week 52, patients will continue to receive BCD-085 120 mg once every 4 weeks starting from Week 54 with injections given at Weeks 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 122, 126, 130, 134, 138, 142, 146, 150, 154.

Patients in Arm 3 will receive placebo as two 1.0 mL SC injections on Day 1 of Week 0, Week 1, Week 2, Week 4, then on Day 1 of Week 6, Week 8, Week 10 inclusive (blinded treatment period). After that, they will be switched to BCD-085 120 mg SC with injections given on Day 1 of Weeks 12, 13, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50. If achieving ≥PASI 75 response at Week 52, patients will continue to receive BCD-085 120 mg once every 4 weeks starting from Week 54 with injections given at Weeks 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, 102, 106, 110, 114, 118, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166.

The patients will be followed up until Week 158 (in Arms 1 and 2) or Week 170 (in Arm 3).

Regardless of the arm where the patient is assigned to, during the main study period (Week 0 through Week 54) SC injections will be performed by an authorized member of the study team at the study site (except for the injection on Week 54).

At Week 54 patients will be trained on how to self-inject the investigational product. If necessary, the training can be repeated at any of the subsequent visits.

During the extension study period (Week 54 to Week 154 for patients from Arms 1 and 2, Week 54 to Week 166 for patients from Arm 3), patients will self-inject the investigational product at home (on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150 in Arms 1 and 2; on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150, 158, 162 in Arm 3) after relevant training at the study site at Week 54. Injections of the investigational product on visit dates will be performed by an authorized member of the study team at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154 (in Arms 1 and 2) or at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154, 166 (in Arm 3). The first self-injection of the investigational

product at Week 54 will be performed under the supervision of an authorized member of the study team.

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. Description of the dosage form, packaging, and labeling of the investigational products

See section 1.2. Name and description of investigational products.

4.4.2.1. Test drug

See Section 1.2.1. **Test drug**

See Section 1.2.2. **Placebo**

4.4.2.3. Labeling of investigational products

See Section 1.2.3.

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

The expected duration of the study is 65 months, which includes patients' recruitment (up to 12 months), treatment period, follow-up period, and data collection and statistical processing. The expected duration of each subject's participation in the study, including the screening period, active study phase and follow-up period, is about 162 weeks (for patients from Arms 1 and 2) or 174 weeks (for patients from Arm 3).

4.6. Description of the sequence and duration of all study periods

4.6.1 Study visits and procedures

The study includes the following periods:

1. Screening (up to 28 days from signing the Patient Information Sheet with the Informed Consent Form, inclusive);
2. Main treatment period (from Week 0 through Week 54;
3. Extension treatment period (from Week 54 through Week 154 in Arms 1 and 2, from Week 54 through Week 166 in Arm 3);

4. Follow-up period (from Week 154 through Week 158 in Arms 1 and 2, from Week 166 through Week 170 in Arm 3).

The Investigator will decide whether it is feasible and possible to include the patient in the extension study period based on efficacy data (PASI 75), tolerability and safety of BCD-085 in each particular patient during the main study period if the patient gives his/her consent to participate in the extension study period. If by the date of approval of Protocol BCD-085-7 version 2.0 of 02-Nov-2018 the patient has completed all visits of the main treatment period, and the last injection of the investigational product at Week 50 was not more than 6 weeks ago, the Investigator should inform the patient about this Amendment and about an opportunity to continue the therapy in the extension study period, and invite the patient to come to the study site for reading and signing the new version of the Informed Consent Form (v. 2.0 as of 02-Nov-2018). If the patient agrees/refuses to visit the study site and/or is lost to follow-up, the investigator should record this in source documentation. If by the date when Protocol BCD-085-7 v. 2.0 of 02-Nov-2018 is approved the patient has not completed the main study period, the Investigator should inform the patient about this Protocol Amendment and an opportunity to participate in the extension study period, and the patient will sign the informed consent form during the planned visit. This should be recorded in the source documentation.

Table 25 lists all the procedures to be performed in the study. All data obtained during these assessments must be confirmed by the source documents.

The screening/baseline assessment should be performed within 28 days before the estimated date of the first infusion of the investigational product. Visit 1 should be within 4 days after the randomization date. Prior results may be used for certain screening tests and exams (see section 4.7 for details). CBC, blood chemistry, urinalysis, QuantiFERON (or T-Spot) can be repeated once at screening. Repeated collection of biospecimens is also allowed if the sample is lost, if any technical problems occur at the pre-analytical phase (defective sampling/storage/transportation of the material), or is the biospecimen is not suitable for analysis (e.g. due to hemolysis or milky serum). At the end of the screening period, the patient should be assessed for the inclusion/exclusion criteria and undergo randomization. The schedule of visits during the extension period is presented in Table 24.

Table 24. Schedule of visits during the extension period.

Arms 1 and 2: patients initially randomized to BCD-085 arms, Arm 3: patients initially randomized to the placebo arm			
Visit	**Group 1**	**Group 2**	**Arm 3**
Visit 23 (Day 1 of Week 62)	+	+	+
Visit 23-1 (Day 1 of Week 64)	Not performed	Not performed	+
Visit 24 (Day 1 of Week 74)	+	+	+
Visit 25 (Day 1 of Week 86)	+	+	+
Visit 26 (Day 1 of Week 98)	+	+	+
Visit 27 (Day 1 of Week 110)	+	+	+
Visit 28 (Day 1 of Week 122)	+	+	+
Visit 29 (Day 1 of Week 134)	+	+	+
Visit 30 (Day 1 of Week 146)	+	+	+
Visit 31 (Day 1 of Week 154)	+	+	+
Visit 32 (Day 1 of Week 158)	+	+	N/A
Visit 32-1 (Day 1 of Week 166)	Not performed	Not performed	+
Visit 32-2 (Day 1 of Week 170)	Not performed	Not performed	+

Table 25. Schedule of procedures and visits during the study (main treatment period, Week 0 to Week 54).

Visit	Screening	1	2	3	4	5	6	7	8	8-1[22]	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	Week -4 to Week 0 (28 days)	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14	Week 16	Week 18	Week 22	Week 24	Week 26	Week 30	Week 34	Week 38	Week 42	Week 46	Week 50	Week 52	Week 54
Day		1	1	1	1±3	1±3	1±3	1±3	1±3	1	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Informed consent form	+																							
Medical history and complaints	+																							
Information about prior (at screening only)/concurrent therapy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood pressure, wrist pulse, and body temperature	+	+[23]	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+		+
Physical examination	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+		+
Height[24] and body weight	+															+								+
Complete blood count	+	+					+		+						+			+		+			+	
Blood chemistry[25]	+	+					+		+						+			+		+				+
hs-CRP	+								+						+								+	

[22] This visit is performed only for Arm 3.
[23] Blood pressure, wrist pulse, and body temperature are measured any time before and immediately after the administration of the investigational product.
[24] The height is measured at screening only.
[25] Alkaline phosphatase is measured at screening only.

Visit	Screening	1	2	3	4	5	6	7	8	8-1[22]	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	Week -4 to Week 0 (28 days)	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14	Week 16	Week 18	Week 22	Week 24	Week 26	Week 30	Week 34	Week 38	Week 42	Week 46	Week 50	Week 52	Week 54
Day		1	1	1	1±3	1±3	1±3	1±3	1±3	1	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Atherogenicity index (TC/HDL-C)	+								+						+								+	
apoB1 / apoA1	+								+						+								+	
HbA1C[26] (only for patients with confirmed diabetes)	+																							
Tests for HIV, HCV, HBV, syphilis	+[27]																							
Tuberculosis diagnostics[28]	+															+								+
Clinical depression score with Beck's depression inventory	+																							+
Urinalysis	+						+		+						+									+
ECG	+								+							+								+

[26] Patients with diabetes mellitus can be included in the study if their glycated hemoglobin is < 8%. To be valid, results should be taken within 3 months before signing the ICF.
[27] Test results for HIV, HCV, HBV, and syphilis obtained within 1 month before signing the ICF are valid at screening.
[28] TB diagnostics can be performed with the skin test (Diaskintest) or blood test (QuantiFERON/T-spot). QuantiFERON/T-spot can be repeated once. Upon reconciliation with the Sponsor, the patient with uncertain Diaskintest/QuantiFERON/T-spot results can be enrolled in the study if the TB Specialist confirms in written that the patient has no TB infection, and the patient shows no signs of active TB according to the chest X-ray performed any time within 3 months before signing the ICF or during the screening. The Diaskintest results are valid if the test was performed within 3 months before signing the ICF.

Visit	Screening	1	2	3	4	5	6	7	8	8-1[22]	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	Week -4 to Week 0 (28 days)	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14	Week 16	Week 18	Week 22	Week 24	Week 26	Week 30	Week 34	Week 38	Week 42	Week 46	Week 50	Week 52	Week 54
Day		1	1	1	1±3	1±3	1±3	1±3	1±3	1	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Chest X-ray[29]	+																							+
Pregnancy test[30]	+																							+
Inclusion/exclusion criteria	+																							
Inclusion in the study (randomization and stratification)	+																							
Administration of the investigational product[31]		+	+	+	+	+	+	+	+[32]	+	+		+	+		+	+	+	+	+	+	+		+[33]
Training on the procedure of subcutaneous injection																								+[33]

[29] 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 3 months before signing the ICF for this study.

[30] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

[31] Injections of the investigational product are given by an authorized healthcare professional directly at the study site, except for Week 54 when the patient self-injects the investigational product under the supervision of an authorized healthcare professional.

[32] The investigational product is administered only to patients from Arm 3.

[33] Only for patients participating in the extension study period.

Visit	Screening	1	2	3	4	5	6	7	8	8-1[22]	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	**Week -4 to Week 0 (28 days)**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 13**	**Week 14**	**Week 16**	**Week 18**	**Week 22**	**Week 24**	**Week 26**	**Week 30**	**Week 34**	**Week 38**	**Week 42**	**Week 46**	**Week 50**	**Week 52**	**Week 54**
Day		1	1	1	1±3	1±3	1±3	1±3	1±3	1	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Dispensing the investigational product[34]																								+[33]
Dispensing the Patient's Diary																								+[33]
Blood drawing for immunogenicity testing		+[35]							+						+									+
Psoriasis area and severity (PASI)	+						+		+			+			+					+			+	
Static Physician's Global Assessment (sPGA)	+						+		+			+			+					+			+	
Nail Psoriasis Severity Index (NAPSI)	+								+						+								+	
Evaluation of psoriatic arthritis: tender/swollen	+								+						+								+	

[34] A container for used syringes is also dispensed.
[35] Blood for immunogenicity study must be collected strictly before the administration of the investigational product.

Visit	Screening	1	2	3	4	5	6	7	8	8-1[22]	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	Week -4 to Week 0 (28 days)	Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14	Week 16	Week 18	Week 22	Week 24	Week 26	Week 30	Week 34	Week 38	Week 42	Week 46	Week 50	Week 52	Week 54
Day		1	1	1	1±3	1±3	1±3	1±3	1±3	1	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
joints counts[36] (66/68)																								
Functional disability index (HAQ-DI)	+								+						+								+	
Assessment of psoriatic arthritis: physician's assessment of arthritis activity (VAS)	+								+						+								+	
Assessment of psoriatic arthritis: patient's assessment of arthritis activity (VAS)	+								+						+								+	
Assessment of psoriatic arthritis: patient's assessment of pain (VAS)	+								+						+								+	
[redacted]																								

[36] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

Visit	Screening	1	2	3	4	5	6	7	8	8-1[22]	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	**Week -4 to Week 0 (28 days)**	**Week 0**	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 13**	**Week 14**	**Week 16**	**Week 18**	**Week 22**	**Week 24**	**Week 26**	**Week 30**	**Week 34**	**Week 38**	**Week 42**	**Week 46**	**Week 50**	**Week 52**	**Week 54**
Day		**1**	**1**	**1**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**	**1±3**
The patient fills out the VAS for itch	+		+						+						+								+	
DLQI questionnaire	+						+		+						+					+			+	
Injection site reactions		+[37]	+	+	+	+	+	+	+[38]	+	+		+	+		+	+	+	+	+	+	+		
Unblinding									+															
Recording AEs/SAEs	+[39]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Assessing the patient for eligibility for the extension study period																								+

[37] Performed twice during Visit 1: 4 h and 8 h after the injections. On other visits the procedure is performed just once (after dosing).
[38] Injection site reactions in patients from Arm 3 at Visit 8 are assessed in 4 and 8 hours after the first administration of BCD-085.
[39] At screening, only serious adverse events should be registered.

Table 26. Schedule of study visits and procedures for Arms 1 and 2 (extension treatment and follow-up periods, Weeks 54 through Week 170, starting from Week 62).

Visit	-	23	-	-	24	-	-	25	-	-	26	-	-
Week	58	62	66	70	74	78	82	86	90	94	98	102	106
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Information about concomitant therapy		+			+			+			+		
Blood pressure, wrist pulse, and body temperature		+			+			+			+		
Physical examination		+			+			+			+		
Body weight								+					
Complete blood count		+			+			+			+		
Blood chemistry		+			+			+			+		
hs-CRP		+						+					
Atherogenicity index (TC/HDL-C)								+					
apoB1 / apoA1								+					
Tuberculosis diagnostics								+					
Urinalysis		+			+			+			+		
ECG													
Pregnancy test		+			+			+			+		
Administration of BCD-085 at the study site		+			+			+			+		
Self-administration of BCD-085 by the patient at home	+		+	+		+	+		+	+		+	+
Dispensing the investigational product[40]		+			+			+			+		
Accounting of the investigational product		+			+			+			+		

[40] A container for used syringes is also dispensed.

Visit	-	23	-	-	24	-	-	25	-	-	26	-	-
Week	58	62	66	70	74	78	82	86	90	94	98	102	106
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Assessing the Patient's Diary		+			+			+			+		
Blood drawing for immunogenicity testing								+					
Psoriasis area and severity (PASI)		+			+			+			+		
Static Physician's Global Assessment (sPGA)		+			+			+			+		
Nail Psoriasis Severity Index (NAPSI)		+			+			+			+		
[redacted]													
The patient fills out the VAS for itch		+			+			+			+		
DLQI questionnaire		+			+			+			+		
Evaluation of psoriatic arthritis: tender/swollen joints counts[41] (66/68)		+						+					
Functional disability index (HAQ-DI)		+						+					
Assessment of psoriatic arthritis: physician's assessment of arthritis activity (VAS)		+						+					
Assessment of psoriatic arthritis: patient's assessment of arthritis activity (VAS)		+						+					
Assessment of psoriatic arthritis: patient's assessment of pain (VAS)		+						+					

[41] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

Visit	-	23	-	-	24	-	-	25	-	-	26	-	-
Week	58	62	66	70	74	78	82	86	90	94	98	102	106
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Injection site reactions		+			+			+			+		
Recording AEs/SAEs		+			+			+			+		

Table 26 (continued).

Visit	27	-	-	28	-	-	29	-	-	30	-	31	32
Week	**110**	**114**	**118**	**122**	**126**	**130**	**134**	**138**	**142**	**146**	**150**	**154**	**158**
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Information about concomitant therapy	+			+			+			+		+	+
Blood pressure, wrist pulse, and body temperature	+			+			+			+		+	+
Physical examination	+			+			+			+		+	+
Body weight							+						+
Complete blood count	+			+			+			+		+	+
Blood chemistry	+			+			+			+		+	+
hs-CRP	+						+					+	
Atherogenicity index (TC/HDL-C)							+						+
apoB1 / apoA1							+						+
Tuberculosis diagnostics	+						+						+
Urinalysis	+			+			+			+		+	+
ECG	+												+
Pregnancy test	+			+			+			+		+	+
Administration of BCD-085 at the study site	+			+			+			+		+	
Self-administration of BCD-085 by the patient at home		+	+		+	+		+	+		+		
Dispensing the investigational product[42]	+			+			+			+			
Accounting of the investigational product	+			+			+			+		+	

[42] A container for used syringes is also dispensed.

Visit	27	-	-	28	-	-	29	-	-	30	-	31	32
Week	110	114	118	122	126	130	134	138	142	146	150	154	158
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Assessing the Patient's Diary	+			+			+			+		+	
Blood drawing for immunogenicity testing	+						+					+	
Psoriasis area and severity (PASI)	+			+			+			+		+	
Static Physician's Global Assessment (sPGA)	+			+			+			+		+	
Nail Psoriasis Severity Index (NAPSI)	+			+			+			+		+	
[redacted]													
The patient fills out the VAS for itch	+			+			+			+		+	
DLQI questionnaire	+			+			+			+		+	
Evaluation of psoriatic arthritis: tender/swollen joints counts[43] (66/68)	+						+					+	
Functional disability index (HAQ-DI)	+						+					+	
Assessment of psoriatic arthritis: physician's assessment of arthritis activity (VAS)	+						+					+	
Assessment of psoriatic arthritis: patient's assessment of arthritis activity (VAS)	+						+					+	

[43] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

Visit	27	-	-	28	-	-	29	-	-	30	-	31	32
Week	110	114	118	122	126	130	134	138	142	146	150	154	158
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Assessment of psoriatic arthritis: patient's assessment of pain (VAS)	+						+					+	
Injection site reactions	+			+			+			+		+	+
Recording AEs/SAEs	+			+			+			+		+	+

Table 27. Schedule of study visits and procedures for Arm 3 (extension treatment and follow-up periods, Weeks 54 through Week 170, starting from Week 62).

Visit	-	23	23-1	-	-	24	-	-	25	-	-	26	-	-	27
Week	58	62	64	66	70	74	78	82	86	90	94	98	102	106	110
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Information about concomitant therapy		+	+			+			+			+			+
Blood pressure, wrist pulse, and body temperature		+	+			+			+			+			+
Physical examination		+	+			+			+			+			+
Body weight									+						
Complete blood count		+	+			+			+			+			+
Blood chemistry		+				+			+			+			+
hs-CRP		+	+						+						+
Atherogenicity index (TC/HDL-C)									+						
apoB1 / apoA1									+						

Visit	-	23	23-1	-	-	24	-	-	25	-	-	26	-	-	27
Week	58	62	64	66	70	74	78	82	86	90	94	98	102	106	110
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Tuberculosis diagnostics									+						+
Urinalysis		+				+			+			+			+
ECG															+
Pregnancy test		+				+			+			+			+
Administration of the investigational product at the study site		+				+			+			+			+
Self-administration of the investigational product at home	+			+	+		+	+		+	+		+	+	
Dispensing the investigational product[44]		+				+			+			+			+
Accounting of the investigational product		+				+			+			+			+
Assessing the Patient's Diary		+				+			+			+			+
Blood drawing for immunogenicity testing			+									+			
Psoriasis area and severity (PASI)		+	+			+			+			+			+

[44] A container for used syringes is also dispensed.

Visit	-	23	23-1	-	-	24	-	-	25	-	-	26	-	-	27
Week	58	62	64	66	70	74	78	82	86	90	94	98	102	106	110
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Static Physician's Global Assessment (sPGA)		+	+			+			+			+			+
Nail Psoriasis Severity Index (NAPSI)		+	+			+			+			+			+
The patient fills out the VAS for itch		+	+			+			+			+			+
DLQI questionnaire		+	+			+			+			+			+
Evaluation of psoriatic arthritis: tender/swollen joints counts[45] (66/68)		+	+						+						+
Functional disability index (HAQ-DI)		+	+						+						+
Assessment of psoriatic arthritis: physician's assessment of arthritis activity (VAS)		+	+						+						+

[45] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

Visit	-	23	23-1	-	-	24	-	-	25	-	-	26	-	-	27
Week	58	62	64	66	70	74	78	82	86	90	94	98	102	106	110
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Assessment of psoriatic arthritis: patient's assessment of arthritis activity (VAS)		+	+						+						+
Assessment of psoriatic arthritis: patient's assessment of pain (VAS)		+	+						+						+
Injection site reactions		+	+			+			+			+			+
Recording AEs/SAEs		+	+			+			+			+			+

Table 27 (continued).

Visit	-	-	28	-	-	29	-	-	30	-	31	-	-	32-1	32-2
Week	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Information about concomitant therapy			+			+			+		+			+	+
Blood pressure, wrist pulse, and body temperature			+			+			+		+			+	+
Physical examination			+			+			+		+			+	+
Body weight						+									+
Complete blood count			+			+			+		+			+	+
Blood chemistry			+			+			+		+			+	+
hs-CRP			+			+					+			+	

Visit	-	-	28	-	-	29	-	-	30	-	31	-	-	32-1	32-2
Week	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
Atherogenicity index (TC/HDL-C)						+									+
apoB1 / apoA1						+									+
Tuberculosis diagnostics						+									+
Urinalysis			+			+			+		+			+	+
ECG															+
Pregnancy test			+			+			+		+			+	+
Administration of the investigational product at the study site			+			+			+		+			+	
Self-administration of the investigational product at home	+	+		+	+		+	+		+		+	+		
Dispensing the investigational product[46]			+			+			+		+				
Accounting of the investigational product			+			+			+		+			+	
Assessing the Patient's Diary			+			+			+		+			+	
Blood drawing for immunogenicity testing			+						+					+	
Psoriasis area and severity (PASI)			+			+			+		+			+	
Static Physician's Global Assessment (sPGA)			+			+			+		+			+	
Nail Psoriasis Severity Index (NAPSI)			+			+			+		+			+	

[46] A container for used syringes is also dispensed.

Visit	-	-	28	-	-	29	-	-	30	-	31	-	-	32-1	32-2
Week	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170
Day	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3	1±3
The patient fills out the VAS for itch			+			+			+		+			+	
DLQI questionnaire			+			+			+		+			+	
Evaluation of psoriatic arthritis: tender/swollen joints counts[47] (66/68)			+			+					+			+	
Functional disability index (HAQ-DI)			+			+					+			+	
Assessment of psoriatic arthritis: physician's assessment of arthritis activity (VAS)			+			+					+			+	
Assessment of psoriatic arthritis: patient's assessment of arthritis activity (VAS)			+			+					+			+	
Assessment of psoriatic arthritis: patient's assessment of pain (VAS)			+			+					+			+	
Injection site reactions			+			+			+		+			+	+
Recording AEs/SAEs			+			+			+		+			+	+

[47] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

Information for the Investigator about allowed changes in scheduled dates of visits

The first visit can be conducted on any day of the week. However, all the subsequent visits must be conducted on the same day of the week, with the intervals specified by the visit schedule. Thus, if Visit 1 ("Day 1 of Week 0") was conducted on Wednesday, all subsequent visits, starting from Visit 2 ("Day 1 of Week 1"), must also be conducted on Wednesdays.

The table below contains information about the allowed changes in the dates of the study visits.

Table 28. Allowed changes in the study visits during **the main study period (Weeks 0 to 54).**

Visit name	Allowed changes	Note
Screening	N/A	N/A
Visit 1 (Day 1 of Week 0)	Not later than 4 days after randomization	-
Visit 2 (Day 1 of Week 1) Visit 3 (Day 1 of Week 2) Visit 4 (Day 1 of Week 4) Visit 5 (Day 1 of Week 6) Visit 6 (Day 1 of Week 8) Visit 7 (Day 1 of Week 10) Visit 8 (Day 1 of Week 12) Visit 8-1[48] (Day 1 of Week 12) Visit 9 (Day 1 of Week 14) Visit 10 (Day 1 of Week 16) Visit 11 (Day 1 of Week 18) Visit 12 (Day 1 of Week 22) Visit 13 (Day 1 of Week 24) Visit 14 (Day 1 of Week 26) Visit 15 (Day 1 of Week 30) Visit 16 (Day 1 of Week 34) Visit 17 (Day 1 of Week 38)	• Due to force-majeure circumstances: not later than in 7 days (inclusive) and not earlier than 3 days before the scheduled date • Due to AE: not later than in 14 days (inclusive)	• If a visit when an injection of the investigational product is scheduled has to be postponed by more than 3 days, all subsequent visits must be re-scheduled accordingly. The first postponement day is the day after the visit date. • If the patient misses this visit, subsequent visits are not re-scheduled. • Other cases of visit re-scheduling must be agreed with the Sponsor. • A severe violation of visit time windows from Week 0 to Week 52 is a postponement of a visit by more than 7 days (inclusive) due to any reasons or by more than 14 days (inclusive) due to AEs. • All cases when visits have to be postponed by more than 7 days (inclusive) due to reasons not related to AEs or by more than 14 days (inclusive) due to AEs must be agreed with the Sponsor.

[48] This visit is performed only for Arm 3.

Visit name	Allowed changes	Note
Visit 18 (Day 1 of Week 42)		
Visit 19 (Day 1 of Week 46)		
Visit 20 (Day 1 of Week 50)		
Visit 21 (Day 1 of Week 52)		
Visit 22 (Day 1 of Week 54)	• The visit can be postponed by up to 21 days (due to any reasons)	• All cases when the visit has to be postponed by more than 21 days (inclusive) due to AEs must be agreed with the Sponsor.

Table 29. Allowed changes in the study visits during **the extension and follow-up periods (Weeks 55 to 170).**

Visit name	Allowed changes	Note
Visit 23 (Day 1 of Week 62)	• Due to force-majeure circumstances: not later than in 7 days (inclusive) and not earlier than 3 days before the scheduled date • Due to AE: not later than in 14 days (inclusive)	• If the date of a visit with the investigational product administration has to be shifted by more than 3 days, dates of the subsequent injections also should be shifted. • If the patient misses this visit, subsequent visits are not re-scheduled. • Other cases of visit re-scheduling must be agreed with the Sponsor. See Section 6.3.1. "Treatment compliance"
Visit 23-1[49] (Day 1 of Week 64)		
Visit 24 (Day 1 of Week 74)	• Due to force-majeure circumstances: not later than in 14 days (inclusive) and not earlier 3 days before the scheduled date	• If the date of a visit with the investigational product administration has to be shifted by more than 3 days, dates of the subsequent injections also should be shifted. • If the patient misses this visit, subsequent visits are not re-scheduled. • Other cases of visit re-scheduling must be agreed with the Sponsor. See Section 6.3.1. "Treatment compliance"
Visit 25 (Day 1 of Week 86)		
Visit 26 (Day 1 of Week 98)		
Visit 27 (Day 1 of Week 110)		
Visit 28 (Day 1 of Week 122)		
Visit 29 (Day 1 of Week 134)		
Visit 30 (Day 1 of Week 146)		
Visit 31 (Day 1 of Week 154)		

[49] Visits 23-1, 32-1, 32-2 are performed only in patients from Arm 3.

Visit name	Allowed changes	Note
Visit 32[50] (Day 1 of Week 158)		
Visit 32-1[51] (Day 1 of Week 166)		
Visit 32-2[51] (Day 1 of Week 170)		

4.6.2. Procedures by visits

Procedures of Screening Period

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

- Taking informed consent from the patient.
- Taking medical history and documenting any patient complaints.
- Collecting information about concomitant therapy (including therapies used within 1 month before signing the ICF).
- Blood pressure, wrist pulse, and body temperature.
- Physical examination (including body weight and height).
- Complete blood count[52] [redacted]
- Bloodchemistry[36] [redacted]
- Determination of hs-CRP (highly-sensitive C-reactive protein), atherogenicity index, apoB1/apoA1 ratio [redacted]
- Glycated hemoglobin HbA1c is measured only in patients with confirmed diabetes mellitus [redacted]
- Tests for HIV, HCV, HBV, and syphilis [redacted]
- Urinalysis[36].
- ECG.

[50] Visit 32 is performed only in patients from Arms 1 and 2.
[51] Visits 32-1, 32-2 are performed only in patients from Arm 3.
[52] At screening, the test can be repeated once, if the first result does not meet the eligibility criteria.

- Chest X-ray[53].
- Pregnancy test[54].
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- The patient fills out the Beck depression inventory.
- For patients with psoriatic arthritis: swollen/tender joint count[55] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- TB test[56] [redacted]
- Checking for eligibility (inclusion/non-inclusion criteria).
- Inclusion in the study (randomization and stratification).
- Recording SAEs.

[redacted]

[53] 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 3 months before signing the informed consent form for this study.
[54] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.
[55] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.
[56] TB diagnostics can be performed with the skin test (Diaskintest) or blood test (QuantiFERON/T-spot). QuantiFERON/T-spot can be repeated once. Upon reconciliation with the Sponsor, the patient with uncertain Diaskintest/QuantiFERON/T-spot results can be enrolled in the study if the TB Specialist confirms in written that the patient has no TB infection, and the patient shows no signs of active TB according to the chest X-ray performed any time within 3 months before signing the ICF or during the screening. The Diaskintest results are valid if the test was performed within 3 months before signing the ICF.

Procedures of Visit 1 (Day 1 of Week 0)

- Physical examination.
- Blood sampling for immunogenicity study (must be done BEFORE the injection of BCD-085/placebo) [redacted]
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Information about concomitant therapy.
- Administration of BCD-085/placebo.
- Blood pressure, wrist pulse, and body temperature are measured any time before and immediately after the administration of the investigational product.
- Assessing injection site reactions (two times): 4 h and 8 h after the injection of BCD-085/placebo.
- Recording AEs/SAEs.

[redacted]

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

- Physical examination.
- The patient fills out the VAS for itch.
- Administration of BCD-085/placebo.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 3 (Day 1 of Week 2)

- Physical examination.
- Administration of BCD-085/placebo.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.

- Recording AEs/SAEs.

Procedures of Visit 4 (Day 1 of Week 4)

- Physical examination.
- Administration of BCD-085/placebo.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 5 (Day 1 of Week 6)

- Physical examination.
- Administration of BCD-085/placebo.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 6 (Day 1 of Week 8)

- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- [redacted]
- DLQI questionnaire.
- Administration of BCD-085/placebo.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Urinalysis.
- Information about concomitant therapy.
- Assessing injection site reactions.

- Recording AEs/SAEs.

[redacted]

Procedures of Visit 7 (Day 1 of Week 10)

- Physical examination.
- Administration of BCD-085/placebo.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 8 (Day 1 of Week 12)

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- Nail Psoriasis Severity Index (NAPSI).
- Assessment of psoriatic arthritis: swollen/tender joint count(66/68), VAS by the patient (pain, disease activity) and by the physician (disease activity), functional activity with HAQ-DI.
- Unblinding.
- Taking a blood sample for immunogenicity assay [redacted]
- Complete blood count [redacted]
- Blood chemistry [redacted]
- hs-CRP, atherogenicity index, apoB1/apoA1 [redacted]
- Urinalysis.

- Administration of BCD-085 (only to patients from Arm 3: first administration of BCD-085).
- Blood pressure, heart rate and body temperature (immediately after dosing).[57]
- ECG.
- Assessing injection site reactions.[58]
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 8-1 (Day 1 of Week 13) (only in patients from Arm 3)

- Physical examination.
- Information about concomitant therapy.
- Second administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 9 (Day 1 of Week 14)

- Physical examination.
- Information about concomitant therapy.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 10 (Day 1 of Week 16)

- Information about concomitant therapy.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- [redacted]

[57] For patients of Arm 3 just after the administration of the investigational product.
[58] In Arm 3, assessment of injection site reactions on Visit 8 (Week 12) is performed 4 h and 8 h after the injection of BCD-085.

- Recording AEs/SAEs.

Procedures of Visit 11 (Day 1 of Week 18)

- Physical examination.
- Information about concomitant therapy.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 12 (Day 1 of Week 22)

- Physical examination.
- Information about concomitant therapy.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 13 (Day 1 of Week 24)

- Information about concomitant therapy.
- Taking a blood sample for immunogenicity assay [redacted]
- hs-CRP, atherogenicity index, apoB1/apoA1 [redacted]
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Urinalysis.

- Assessing psoriatic arthritis: swollen/tender joint count (66/68), VAS by the patient (pain, disease activity) and by the physician (disease activity), functional activity with HAQ-DI.
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 14 (Day 1 of Week 26)

- Physical examination (including body weight).
- TB test[59] [redacted]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- ECG.
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 15 (Day 1 of Week 30)

- Physical examination.
- Information about concomitant therapy.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Assessing injection site reactions.
- Recording AEs/SAEs.

[59]If the patient has to take a Diaskintest, he/she will receive a referral for the test on this Visit. The Diaskintest must be performed within 7 days after the referral. If the TB test show uncertain/positive results, the patient should be called to the study site for an unscheduled visit where he/she will be given a referral to a TB clinic. If the TB is confirmed, this must be registered as an AE, and the patient must be withdrawn from the study. Patients can continue the study if the TB Specialist provides a documented impression that the patient has no TB infection (the blood work for TB may be repeated on the discretion of the TB Specialist).

Procedures of Visit 16 (Day 1 of Week 34)

- Complete blood count [redacted]
- Blood chemistry [redacted]
- Physical examination.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 17 (Day 1 of Week 38)

- Physical examination.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 18 (Day 1 of Week 42)

- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- [redacted]
- DLQI questionnaire.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.

- Assessing injection site reactions.
- Recording AEs/SAEs.

Total blood volume drawn at the visit: 12.5 mL.

Procedures of Visit 19 (Day 1 of Week 46)

- Physical examination.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 20 (Day 1 of Week 50)

- Physical examination.
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Information about concomitant therapy.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Procedures of Visit 21 (Day 1 of Week 52)

- Information about concomitant therapy.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- Nail Psoriasis Severity Index (NAPSI).
- Assessing psoriatic arthritis: swollen/tender joint count (66/68), VAS by the patient (pain, disease activity) and by the physician (disease activity), functional activity with HAQ-DI.

- hs-CRP, atherogenicity index, apoB1/apoA1 [redacted]
- Complete blood count [redacted]
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 22 (Day 1 of Week 54)

- Assessing the patient for eligibility for the extension study period.
- Physical examination (including body weight).
- Taking a blood sample for immunogenicity assay [redacted].
- Blood chemistry [redacted].
- Urinalysis.
- Pregnancy test.
- ECG.
- TB test (skin test (Diaskintest) or blood test [redacted]
- The patient fills out Beck depression inventory.
- Chest X-ray.
- Blood pressure, wrist pulse, and body temperature.
- Information about concomitant therapy.
- Recording AEs/SAEs.

If the patient continues to participate in the extension study period:

- Training the patient on self-administration of the investigational product, fulfilling the Diary, requirements for investigational product transportation (in a cooling bag with cold packs) and storage, requirements for handling with used syringes and returning the syringes and the Diary.
- Self-administration of BCD-085 (under the supervision of an authorized member of the study team).
- Dispensing the investigational product for self-administration and a container for used syringes.
- Dispensing the Patient's Diary.

Procedures of Visit 23 (Day 1 of Week 62)

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA)
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- For patients with psoriatic arthritis: swollen/tender joint count[60] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- hs-CRP [redacted]
- Urinalysis.
- Pregnancy test.[61]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes.
- Assessing injection site reactions.
- Recording AEs/SAEs.

[60] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.
[61] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

Procedures of Visit 23-1 (Day 1 of Week 64) This visit is performed only for patients from Arm 3.

- Information about concomitant therapy.
- Blood pressure, wrist pulse, and body temperature (any time).
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- For patients with psoriatic arthritis: swollen/tender joint count[62] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- Complete blood count [redacted]
- hs-CRP [redacted]
- Taking a blood sample for immunogenicity assay [redacted]
- Assessing injection site reactions.
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 24 (Day 1 of Week 74)

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).

[62] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

- Static Physician's Global Assessment (sPGA).
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Urinalysis.
- Pregnancy test.[63]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes
- Assessing injection site reactions.
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 25 (Day 1 of Week 86)

- Information about concomitant therapy.
- Physical examination (including body weight).
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.

[63] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- For patients with psoriatic arthritis: swollen/tender joint count[64] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- hs-CRP, atherogenicity index, apoB1/apoA1 [redacted]
- TB test (skin test (Diaskintest) or blood test [redacted]
- Chest X-ray.[65]
- Urinalysis.
- Pregnancy test.[66]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Only for patients from Arms 1 and 2:

- Taking a blood sample for immunogenicity assay [redacted]

[redacted]

Procedures of Visit 26 (Day 1 of Week 98)

[64] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.
[65] Performed in patients with positive results of the skin test (Diaskintest) or blood test for TB (QuantiFERON or T-spot).
[66] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- Nail Psoriasis Severity Index (NAPSI).
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Urinalysis.
- Pregnancy test.[67]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Only for patients from Arm 3:

Taking a blood sample for immunogenicity assay [redacted]

[redacted]

Procedures of Visit 27 (Day 1 of Week 110)

- Information about concomitant therapy.
- Physical examination.

[67] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA)
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- For patients with psoriatic arthritis: swollen/tender joint count[68] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- hs-CRP [redacted]
- TB test [redacted]
- Urinalysis.
- Pregnancy test.[69]
- ECG.
- Chest X-ray.[70]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes.

[68] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.
[69] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.
[70] Performed in patients with positive results of the skin test (Diaskintest) or blood test for TB (QuantiFERON or T-spot).

- Assessing injection site reactions.
- Recording AEs/SAEs.

Only for patients from Arms 1 and 2:

- Taking a blood sample for immunogenicity assay [redacted]

[redacted]

Procedures of Visit 28 (Day 1 of Week 122)

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA).
- Nail Psoriasis Severity Index (NAPSI).
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Urinalysis.
- Pregnancy test.[71]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Only for patients from Arm 3:

[71] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- For patients with psoriatic arthritis: swollen/tender joint count[72] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- hs-CRP [redacted]
- Taking a blood sample for immunogenicity assay [redacted]

[redacted]

Procedures of Visit 29 (Day 1 of Week 134)

- Information about concomitant therapy.
- Physical examination (including body weight).
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA)
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- For patients with psoriatic arthritis: swollen/tender joint count[73] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- hs-CRP, atherogenicity index, apoB1/apoA1 [redacted]

[72] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.
[73] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

- TB test [redacted]
- Chest X-ray.[74]
- Urinalysis.
- Pregnancy test.[75]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Only for patients from Arms 1 and 2:

- Taking a blood sample for immunogenicity assay [redacted]

[redacted]

Procedures of Visit 30 (Day 1 of Week 146)

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA)
- Nail Psoriasis Severity Index (NAPSI).
- The patient fills out the VAS for itch.
- DLQI questionnaire.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.

[74] Performed in patients with positive results of the skin test (Diaskintest) or blood test for TB (QuantiFERON or T-spot).
[75] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- Complete blood count [redacted]
- Blood chemistry [redacted]
- Urinalysis.
- Pregnancy test.[76]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Dispensing the investigational product for self-administration and a container for used syringes.
- Assessing injection site reactions.
- Recording AEs/SAEs.

Only for patients from Arm 3:

- Taking a blood sample for immunogenicity assay [redacted]

[redacted]

Procedures of Visit 31 (Day 1 of Week 154)

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA)
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.

[76] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- For patients with psoriatic arthritis: swollen/tender joint count[77] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- hs-CRP [redacted]
- Urinalysis.
- Pregnancy test.[78]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Assessing injection site reactions.
- Recording AEs/SAEs.

Only for patients from Arm 3:

- Dispensing BCD-085 to the patient.

Only for patients from Arms 1 and 2:

- Taking a blood sample for immunogenicity assay [redacted]

[redacted]

Procedures of Visit 32 (Day 1 of 158) The visit is performed only in patients from Arms 1 and 2.

- Information about concomitant therapy.
- Blood pressure, wrist pulse, and body temperature (any time).
- Physical examination (including body weight).
- Complete blood count [redacted]

[77] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.
[78] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- Blood chemistry [redacted]
- Atherogenicity index, apoB1/apoA1 [redacted]
- TB test [redacted]
- Urinalysis.
- Pregnancy test.[79]
- ECG.
- Chest X-ray. [80]
- Assessing injection site reactions.
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 32-1 (Day 1 of Week 166) This visit is performed only for patients from Arm 3.

- Information about concomitant therapy.
- Physical examination.
- Psoriasis Area and Severity Index (PASI), including Body Surface Area affected by psoriasis (BSA).
- Static Physician's Global Assessment (sPGA)
- Nail Psoriasis Severity Index (NAPSI).
- [redacted]
- The patient fills out the VAS for itch.
- DLQI questionnaire.

[79] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.
[80] Performed in patients with positive results of the skin test (Diaskintest) or blood test for TB (QuantiFERON or T-spot).

- For patients with psoriatic arthritis: swollen/tender joint count[81] (66/68), VAS filled out by the patient (pain, disease activity) and by the physician (disease activity), function assessment with HAQ-DI.
- Checking the Patient's Diary and withdrawing a detachable page.
- Accounting of the investigational product.
- Complete blood count [redacted]
- Blood chemistry [redacted]
- hs-CRP [redacted]
- Taking a blood sample for immunogenicity assay [redacted]
- Urinalysis.
- Pregnancy test.[82]
- Administration of BCD-085.
- Blood pressure, heart rate and body temperature (immediately after dosing).
- Assessing injection site reactions.
- Recording AEs/SAEs.

[redacted]

Procedures of Visit 32-2 (Day 1 of Week 170) This visit is performed only for patients from Arm 3.

- Information about concomitant therapy.
- Blood pressure, wrist pulse, and body temperature (any time).
- Physical examination (including body weight).
- Complete blood count [redacted]
- Blood chemistry [redacted]
- Atherogenicity index, apoB1/apoA1 [redacted]

[81] Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.
[82] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.

- TB test (skin test (Diaskintest) or blood test [redacted]
- Urinalysis.
- Pregnancy test.[83]
- ECG.
- Chest X-ray.[84]
- Assessing injection site reactions.
- Recording AEs/SAEs.

[redacted]

During unscheduled visits, the investigator must record AEs/SAEs. Other procedures are at 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 30.

Table 30. Frequency of 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	×30 (for Arms 1 and 2) and 33 (for Arm 3): 1. Screening 2. Day 1 of Week 0 3. Day 1 of Week 1 4. Day 1 of Week 2 5. Day 1 of Week 4 6. Day 1 of Week 6 7. Day 1 of Week 8 8. Day 1 of Week 10	Study site

[83] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.
[84] Performed in patients with positive results of the skin test (Diaskintest) or blood test for TB (QuantiFERON or T-spot).

Test	Tested variable	Frequency	Where the test is performed
		9. Day 1 of Week 12 10. Day 1 of Week 13 (only for Arm 3) 11. Day 1 of Week 14 12. Day 1 of Week 18 13. Day 1 of Week 22 14. Day 1 of Week 26 15. Day 1 of Week 30 16. Day 1 of Week 34 17. Day 1 of Week 38 18. Day 1 of Week 42 19. Day 1 of Week 46 20. Day 1 of Week 50 21. Day 1 of Week 54 22. Day 1 of Week 62 23. Day 1 of Week 64 (only for Arm 3) 24. Day 1 of Week 74 25. Day 1 of Week 86 26. Day 1 of Week 98 27. Day 1 of Week 110 28. Day 1 of Week 122 29. Day 1 of Week 134 30. Day 1 of Week 146 31. Day 1 of Week 154 32. Day 1 of Week 158 (only for patients from Arms 1 and 2) 33. Day 1 of Week 166 (only for Arm 3) 34. Day 1 of Week 170 (only for Arm 3)	
Height and body weight	• Height, cm	×1: at screening	Study site
	• Body weight, kg	×6: 1. At screening 2. Day 1 of Week 26 3. Day 1 of Week 54 4. Day 1 of Week 86 5. Day 1 of Week 134 6. Day 1 of Week 158 (only for patients from Arms 1 and 2) 7. Day 1 of Week 170 (only for Arm 3)	

Test	Tested variable	Frequency	Where the test is performed
Vital signs	• BP, mm Hg • Wrist pulse, bpm • Body temperature (axillary), °C	×31 (for Arms 1 and 2) and ×34 (for Arm 3): 1. Screening 2. Day 1, Week 0 (twice – before and after the injection of investigational product) 3. Day 1 of Week 1 4. Day 1 of Week 2 5. Day 1 of Week 4 6. Day 1 of Week 6 7. Day 1 of Week 8 8. Day 1 of Week 10 9. Day 1 of Week 12 10. Day 1 of Week 13 (only for Arm 3) 11. Day 1 of Week 14 12. Day 1 of Week 18 13. Day 1 of Week 22 14. Day 1 of Week 26 15. Day 1 of Week 30 16. Day 1 of Week 34 17. Day 1 of Week 38 18. Day 1 of Week 42 19. Day 1 of Week 46 20. Day 1 of Week 50 21. Day 1 of Week 54 22. Day 1 of Week 62 23. Day 1 of Week 64 (only for Arm 3) 24. Day 1 of Week 74 25. Day 1 of Week 86 26. Day 1 of Week 98 27. Day 1 of Week 110 28. Day 1 of Week 122 29. Day 1 of Week 134 30. Day 1 of Week 146 31. Day 1 of Week 154 32. Day 1 of Week 158 (only for patients from Arms 1 and 2)	Study site

Test	Tested variable	Frequency	Where the test is performed
		33. Day 1 of Week 166 (only for Arm 3) 34. Day 1 of Week 170 (only for Arm 3)	
Complete blood count	• Hemoglobin (g/L) • Erythrocytes ($\times 10^{12}$/L) • Platelets ($\times 10^{9}$/L) • Leukocytes ($\times 10^{9}$/L) • Neutrophils ($\times 10^{9}$/L) • Lymphocytes ($\times 10^{9}$/L) • Monocytes ($\times 10^{9}$/L) • ESR [85] (mm/h) (blood volume: 3.5 mL)	×18 (for Arms 1 and 2) and ×20 (for Arm 3): 1. Screening 2. Day 1 of Week 0 3. Day 1 of Week 8 4. Day 1 of Week 12 5. Day 1 of Week 24 6. Day 1 of Week 34 7. Day 1 of Week 42 8. Day 1 of Week 52 9. Day 1 of Week 62 10. Day 1 of Week 64 (only for Arm 3) 11. Day 1 of Week 74 12. Day 1 of Week 86 13. Day 1 of Week 98 14. Day 1 of Week 110 15. Day 1 of Week 122 16. Day 1 of Week 134 17. Day 1 of Week 146 18. Day 1 of Week 154 19. Day 1 of Week 158 (only for patients from Arms 1 and 2) 20. Day 1 of Week 166 (only for Arm 3) 21. Day 1 of Week 170 (only for Arm 3)	Study site/central lab
Blood chemistry	• Glucose (mmol/L), • Bilirubin total (µmol/L), • ALT (U/L), • AST (U/L), • Total protein (g/L), • Creatinine (µmol/L). • Alkaline phosphatase (U/L); measured at screening only.	×18 (for Arms 1 and 2) and ×19 (for Arm 3): 1. Screening 2. Day 1 of Week 0 3. Day 1 of Week 8 4. Day 1 of Week 12 5. Day 1 of Week 24 6. Day 1 of Week 34 7. Day 1 of Week 42 8. Day 1 of Week 54	Study site/central lab

[85] Westergren or capillary photometry

Test	Tested variable	Frequency	Where the test is performed
	(blood volume: 9 mL)	9. Day 1 of Week 62 10. Day 1 of Week 74 11. Day 1 of Week 86 12. Day 1 of Week 98 13. Day 1 of Week 110 14. Day 1 of Week 122 15. Day 1 of Week 134 16. Day 1 of Week 146 17. Day 1 of Week 154 18. Day 1 of Week 158 (only for patients from Arms 1 and 2) 19. Day 1 of Week 166 (only for Arm 3) 20. Day 1 of Week 170 (only for Arm 3)	
Highly-sensitive C-reactive protein	• hs-CRP, mg/L	×9 (for Arms 1 and 2) and ×12 (for Arm 3): 1. Screening 2. Day 1 of Week 12 3. Day 1 of Week 24 4. Day 1 of Week 52 5. Day 1 of Week 62 6. Day 1 of Week 64 (only for Arm 3) 7. Day 1 of Week 86 8. Day 1 of Week 110 9. Day 1 of Week 122 (only for Arm 3) 10. Day 1 of Week 134 11. Day 1 of Week 154 12. Day 1 of Week 166 (only for Arm 3)	Study site/central lab
Atherogenicity index, apoB1/apoA1	• Total cholesterol (mmol/L) • HDL (mmol/L) • Total cholesterol/HDL-C ratio • Apolipoprotein B1 (g/L) • Apolipoprotein A1 (g/L)	×7: 1. Screening 2. Day 1 of Week 12 3. Day 1 of Week 24 4. Day 1 of Week 52 5. Day 1 of Week 86 6. Day 1 of Week 134 7. Day 1 of Week 158 (only for patients from Arms 1 and 2)	Study site/central lab

Test	Tested variable	Frequency	Where the test is performed
	• apoB1/apoA1 (blood volume: 4 mL)	8. Day 1 of Week 170 (only for Arm 3)	
Glycated hemoglobin HbA1C (only for patients with suspected/confirmed diabetes mellitus)	• Concentration of HbA1C (%)	×1: at screening	Study site/central lab
Serological tests[86]	• HIV antibodies and antigen p24 (Ag/Ab Combo), • anti-HCV, • HBsAg, anti-HBcor total • Microprecipitation reaction (RPR) or direct agglutination assay for T. pallidum[87]. (blood volume: 10 mL) Additional examinations[88]: • Qualitative PCR for HCV RNA • Qualitative PCR for HBV DNA, anti-HbCor IgM and anti-HbCor IgG (blood volume: 10 mL) • The Dermatology/Venereology Specialist can request additional tests from the following list: specific tests for syphilis – $ELISA_{total}$ [or	×1: at screening	Study site/central lab

[86] HIV, HBV, HCV, and syphilis test results are considered valid for screening if they are obtained within 1 month before signing the ICF and if the test fully meets the requirements of this Protocol.
[87] Other tests can also be used.
[88] Additional examinations are performed if anti-HCV or anti-HbCor (IgM + IgG) have been detected in blood or in case of a positive reaction for syphilis (microprecipitation or direct hemagglutination to *T. pallidum*).

Test	Tested variable	Frequency	Where the test is performed
	ELISA(IgG)+ELISA(IgM)] (blood volume: 6 mL) or immunofluorescence reaction with absorption (blood volume: 6 mL) or T. pallidum immobilization test (blood volume: 6 mL); non-specific test for syphilis – repeat the microprecipitation test (blood volume: 2 mL) or VDRL (blood volume: 2 mL). Other tests can also be used.		
Urinalysis.	• General properties (color, clarity, specific gravity, pH, protein, glucose); • Urinary sediment microscopy (epithelium, erythrocytes, leukocytes, cylinders, bacteria, salts).	×15 (for Arms 1 and 2) and 16 (for Arm 3): 1. Screening 2. Day 1 of Week 8 3. Day 1 of Week 12 4. Day 1 of Week 24 5. Day 1 of Week 54 6. Day 1 of Week 62 7. Day 1 of Week 74 8. Day 1 of Week 86 9. Day 1 of Week 98 10. Day 1 of Week 110 11. Day 1 of Week 122 12. Day 1 of Week 134 13. Day 1 of Week 146 14. Day 1 of Week 154 15. Day 1 of Week 158 (only for patients from Arms 1 and 2) 16. Day 1 of Week 166 (only for Arm 3) 17. Day 1 of Week 170 (only for Arm 3)	Study site/central lab

Test	Tested variable	Frequency	Where the test is performed
Pregnancy test.[89]	• HCG in the urea	×12 (for Arms 1 and 2) and 13 (for Arm 3): 1. Screening 2. Day 1 of Week 54 3. Day 1 of Week 62 4. Day 1 of Week 74 5. Day 1 of Week 86 6. Day 1 of Week 98 7. Day 1 of Week 110 8. Day 1 of Week 122 9. Day 1 of Week 134 10. Day 1 of Week 146 11. Day 1 of Week 154 12. Day 1 of Week 158 (only for patients from Arms 1 and 2) 13. Day 1 of Week 166 (only for Arm 3) 14. Day 1 of Week 170 (only for Arm 3)	Study site
Instrumental examinations	• 12-lead ECG	×6: 1. Screening 2. Day 1 of Week 12 3. Day 1 of Week 26 4. Day 1 of Week 54 5. Day 1 of Week 110 6. Day 1 of Week 158 (only for patients from Arms 1 and 2) 7. Day 1 of Week 170 (only for Arm 3)	Study site/third-party contractors
	• Chest X-ray.[90]	×6: 1. At screening 2. Day 1 of Week 54 3. Day 1 of Week 86[91] 4. Day 1 of Week 110[91]	Study site/third-party contractors

[89] Pregnancy test detecting hCG in the urine (test strips). Pregnancy test is not required if the female patient is at least 2 years post-menopausal or had a uterus or ovary surgery that makes pregnancy impossible.
[90] The test is not required if the patient provides results of chest X-ray/fluorography/CT/MRI performed within 3 months before inclusion in the study.
[91] Performed in patients with positive results of the skin test (Diaskintest) or blood test for TB (QuantiFERON or T-spot).

Test	Tested variable	Frequency	Where the test is performed
		5. Day 1 of Week 134[91] 6. Day 1 of Week 158 (only for patients from Arms 1 and 2)[91] 7. Day 1 of Week 170 (only for Arm 3)[91]	
Immunogenicity assessment	• BAbs and NAbs in the serum (blood volume: 9 mL)	×8 (for Arms 1 and 2) and 9 (for Arm 3): 1. IG1 – Day 1 of Week 0, blood must be drawn before the injection of the investigational product 2. IG2 – Day 1 of Week 12 3. IG3 – Day 1 of Week 24 4. IG4 – Day 1 of Week 54 5. IG4-1 – Day 1 of Week 64[92] 6. IG5 – Day 1 of Week 86[93] or Day 1 of Week 98[92] 7. IG6 – Day 1 of Week 110[93] or Day 1 of Week 122[92] 8. IG7 – Day 1 of Week 134[93] or Day 1 of Week 146[92] 9. IG8 – Day 1 of Week 154[93] or Day 1 of Week 166[92]	Separate subdivision of JSC BIOCAD (central laboratory)
Tuberculosis diagnostics	• Diaskintest **OR**	×7: 1. At screening 2. Day 1 of Week 26[94]	Study center/central lab/third-

[92] Only for patients from Arm 3.
[93] Only for patients from Arms 1 and 2.
[94] If the patient has to take a Diaskintest, at Visit 14 he/she will receive a referral for the test. The Diaskintest must be performed within 7 days after the referral. If the TB test show uncertain/positive results, the patient should be called to the study site for an unscheduled visit where he/she will be given a referral to a TB clinic. If the TB is confirmed,

Test	Tested variable	Frequency	Where the test is performed
	• Blood test for TB infection (QuantiFERON **or** T-spot)	3. Day 1 of Week 54 4. Day 1 of Week 86 5. Day 1 of Week 110 6. Day 1 of Week 134 7. Day 1 of Week 158 (only for patients from Arms 1 and 2) 8. Day 1 of Week 170 (only for Arm 3)	party contractors
Psoriasis area and severity (PASI), body surface area affected by psoriasis (BSA)	• Total score reflecting the extent and area of psoriasis	×16 (for Arms 1 and 2) and 18 (for Arm 3): 1. Screening 2. Day 1 of Week 8 3. Day 1 of Week 12 4. Day 1 of Week 16 5. Day 1 of Week 24 6. Day 1 of Week 42 7. Day 1 of Week 52 8. Day 1 of Week 62 9. Day 1 of Week 64 (only for Arm 3) 10. Day 1 of Week 74 11. Day 1 of Week 86 12. Day 1 of Week 98 13. Day 1 of Week 110 14. Day 1 of Week 122 15. Day 1 of Week 134 16. Day 1 of Week 146 17. Day 1 of Week 154 18. Day 1 of Week 166 (only for Arm 3)	Study site
Static Physician's Global Assessment (sPGA)	• Severity of psoriasis symptoms	×16 (for Arms 1 and 2) and 18 (for Arm 3): 1. Screening 2. Day 1 of Week 8 3. Day 1 of Week 12 4. Day 1 of Week 16 5. Day 1 of Week 24 6. Day 1 of Week 42 7. Day 1 of Week 52	Study site

this must be registered as an AE, and the patient must be withdrawn from the study. Patients can continue the study if the TB Specialist provides a documented impression that the patient has no TB infection (the blood work for TB may be repeated on the discretion of the TB Specialist).

Test	Tested variable	Frequency	Where the test is performed
		8. Day 1 of Week 62 9. Day 1 of Week 64 (only for Arm 3) 10. Day 1 of Week 74 11. Day 1 of Week 86 12. Day 1 of Week 98 13. Day 1 of Week 110 14. Day 1 of Week 122 15. Day 1 of Week 134 16. Day 1 of Week 146 17. Day 1 of Week 154 18. Day 1 of Week 166 (only for Arm 3)	
Nail Psoriasis Severity Index (NAPSI)	• Score for nail matrix and nail bed involvement	×13 (for Arms 1 and 2) and 15 (for Arm 3): 1. Screening 2. Day 1 of Week 12 3. Day 1 of Week 24 4. Day 1 of Week 52 5. Day 1 of Week 62 6. Day 1 of Week 64 (only for Arm 3) 7. Day 1 of Week 74 8. Day 1 of Week 86 9. Day 1 of Week 98 10. Day 1 of Week 110 11. Day 1 of Week 122 12. Day 1 of Week 134 13. Day 1 of Week 146 14. Day 1 of Week 154 15. Day 1 of Week 166 (only for Arm 3)	Study site
Itch assessed by the patient	• 0-100 mm, where 0 refers to no itch and 100 refers to unbearable itch	×14 (for Arms 1 and 2) and 16 (for Arm 3): 1. Screening 2. Day 1 of Week 1 3. Day 1 of Week 12 4. Day 1 of Week 24 5. Day 1 of Week 52 6. Day 1 of Week 62 7. Day 1 of Week 64 (only for Arm 3) 8. Day 1 of Week 74 9. Day 1 of Week 86	Study site

Test	Tested variable	Frequency	Where the test is performed
		10. Day 1 of Week 98 11. Day 1 of Week 110 12. Day 1 of Week 122 13. Day 1 of Week 134 14. Day 1 of Week 146 15. Day 1 of Week 154 16. Day 1 of Week 166 (only for Arm 3)	
[redacted]			
Severity of psoriatic arthritis	• Tender/swollen joints counts (66/68) • Functional disability index (HAQ-DI) • Patient fills out VAS (pain, disease activity) • Physician fills out VAS (disease activity)	×10 (for Arms 1 and 2) and ×12 (for Arm 3): 1. At screening 2. Day 1 of Week 12 3. Day 1 of Week 24 4. Day 1 of Week 52 5. Day 1 of Week 62 6. Day 1 of Week 64 (only for Arm 3) 7. Day 1 of Week 86 8. Day 1 of Week 110 9. Day 1 of Week 122 (only for Arm 3) 10. Day 1 of Week 134 11. Day 1 of Week 154 12. Day 1 of Week 166 (only for Arm 3)	Study site

Test	Tested variable	Frequency	Where the test is performed
Assessing injection site reactions.	• Any injection-site reaction (yes/no)	×29 (for Arms 1 and 2) and ×33 (for Arm 3): 1-2. Day 1 of Week 0 (4 h and 8 h after the injection of BCD-085/placebo) 3. Day 1 of Week 1 4. Day 1 of Week 2 5. Day 1 of Week 4 6. Day 1 of Week 6 7. Day 1 of Week 8 8. Day 1 of Week 10 9. Day[95] 1 of Week 12 10. Day 1 of Week 13 (only for Arm 3) 11. Day 1 of Week 14 12. Day 1 of Week 18 13. Day 1 of Week 22 14. Day 1 of Week 26 15. Day 1 of Week 30 16. Day 1 of Week 34 17. Day 1 of Week 38 18. Day 1 of Week 42 19. Day 1 of Week 46 20. Day 1 of Week 50 21. Day 1 of Week 62 22. Day 1 of Week 64 (only for Arm 3) 23. Day 1 of Week 74 24. Day 1 of Week 86 25. Day 1 of Week 98 26. Day 1 of Week 110 27. Day 1 of Week 122 28. Day 1 of Week 134 29. Day 1 of Week 146 30. Day 1 of Week 154 31. Day 1 of Week 158 32. Day 1 of Week 166 (only for Arm 3) 33. Day 1 of Week 170 (only for Arm 3)	Study site

[95] In Arm 3, assessment of injection site reactions on Visit 8 (Week 12) is performed 4 h and 8 h after the injection of BCD-085.

Test	Tested variable	Frequency	Where the test is performed
Assessing patient's clinical depression with the Beck's depression inventory	• Total score showing the mental state of the patient	×2: 1. Screening 2. Day 1 of Week 54	Study site
Quality of life	DLQI questionnaire	×15 (for Arms 1 and 2) and ×17 (for Arm 3): 1. Screening 2. Day 1 of Week 8 3. Day 1 of Week 12 4. Day 1 of Week 24 5. Day 1 of Week 42 6. Day 1 of Week 52 7. Day 1 of Week 62 8. Day 1 of Week 64 (only for Arm 3) 9. Day 1 of Week 74 10. Day 1 of Week 86 11. Day 1 of Week 98 12. Day 1 of Week 110 13. Day 1 of Week 122 14. Day 1 of Week 134 15. Day 1 of Week 146 16. Day 1 of Week 154 17. Day 1 of Week 166 (only for Arm 3)	Study site

4.7.1. History taking, complaints, demographics

The following data should be recorded at screening:

- Date of birth
- Sex
- Age
- Race
- Reproductive potential [use of contraception (specify which measures), menopause state, its duration, sterilization, if applicable]
- Medical history – past/concomitant diseases (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 – main disease (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 within the last 6 months, 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 reason for discontinuation (if applicable). Medications for the treatment of psoriasis that the patient uses now or has been using within 6 months 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, Weeks 26, 54, 86, 134, 158[96] and 170[97])
- Skin and mucosa (visual examination, describe all pathological changes that are not due to psoriasis)
- Ear-nose-throat, respiratory system (examination, lung auscultation)
- Cardiovascular system (heart auscultation, examination of major vessels area)
- GI (examination, palpation of the abdominal area)
- Palpation of the liver
- Palpation of the spleen

4.7.3. Vital signs

Vital signs include axillary body temperature (°C), blood pressure (on one arm, mm Hg), and heart rate (wrist pulse, bpm).

[96] Only for patients from Arms 1 and 2.
[97] Only for patients from Arm 3.

Blood pressure, pulse, and body temperature at Visit 1 (measured any time before and immediately after the injection of the investigational product).

4.7.4. Laboratory tests

Laboratory investigations include complete blood count, blood chemistry, hs-CRP, atherogenicity index and apoB1/apoA1, TB diagnostics with QuantiFERON/T-spot, blood sampling for immunogenicity testing, urinalysis. In addition, markers of HIV, hepatitis B and C, and syphilis will be determined at screening.

The Protocol allows repeating the CBC and urinalysis once during the screening.

Repeated collection of biospecimens is also allowed if the sample is lost, if any technical problems occur at the pre-analytical phase (defective sampling/storage/transportation of the material), or is the biospecimen is not suitable for analysis (e.g. due to hemolysis or milky serum).

4.7.4.1. Complete blood count

CBC is tested in accordance with the standard procedure. The test is performed at fasting (fasting means at least 8 hours after the last meal). This study includes the following CBC parameters:

- Hemoglobin (g/L)
- Erythrocytes ($\times 10^{12}$/L)
- Leukocytes ($\times 10^{9}$/L)
- Platelets ($\times 10^{9}$/L)
- Neutrophils ($\times 10^{9}$/L)
- Lymphocytes ($\times 10^{9}$/L)
- Monocytes ($\times 10^{9}$/L)
- ESR (mm/h) by Westergren or capillary photometry

[redacted]

Blood sampling is performed using standard procedures.

[redacted]

The specimens are shipped at +2 to +8 °C.

4.7.4.2. Blood chemistry

Blood chemistry is performed according to the standard procedure in 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),
- ALT (U/L),
- AST (U/L),
- Total protein (g/L),
- Creatinine (µmol/L)
- Alkaline phosphatase (U/L), measured at screening only.

[redacted].

Blood sampling is performed using standard procedures.

[redacted]

The specimens are shipped at +2 to +8 °C.

4.7.4.3. Determination of hs-CRP, atherogenicity index, apoB1/apoA1

To assess cardiovascular risks in study subjects, changes over time in highly-sensitive C-reactive protein, atherogenicity index and apoB1/apoA1 ratio will be determined. Concentration of highly-sensitive C-reactive protein will be used to assess psoriatic arthritis according to the ACR criteria. The investigations are performed at fasting state (12 hours without food, including sweet and alcohol beverages, do not smoke for 30 min before blood collecting) from one blood specimen. [redacted]

The atherogenicity index is calculated using total cholesterol (tCs) and high-density lipoproteins (hd-LPP). The apoB1/apoA1 ratio is calculated using levels of apolipoproteins A1 and B1.

Concentration of hs-CRP is measured using latex-enhanced immunoturbidimetry. Concentration of total cholesterol is measured by CHOD/PAP assay. Concentration of HDL is measured also by CHOD/PAP assay but without sample precipitation. Concentration of apolipoproteins B1 and A1 is measured by immunoturbidimetry.

[redacted]

4.7.4.4. Serological tests

The test for HIV-infection detects antibodies to HIV-1, HIV-2, and p24 antigen (HIV Ag/Ab Combo) in the serum or plasma.

The test for syphilis is performed as a microprecipitation (RPR-test) and direct hemagglutination assay. Other tests can also be used. If any of the tests shows positive results, other methods can be used to clarify the diagnosis. In this case, the actions must be reconciled with the Sponsor, and a consultation from a Dermatology/Venereology Specialist is required. The Dermatology/Venereology Specialist can request additional tests from the following list: specific tests for syphilis [redacted]; non-specific tests for syphilis: [redacted] Other tests can also be used.

The screening for HBV includes tests for HBsAg and total antibodies to HBcor antigen (anti-HBcor total = IgG + IgM). If the test results for these markers (HBsAg and anti-HBcor total) are negative, the patient is considered eligible for the study by this criterion. If the patient tests positive for HBsAg, the patient cannot be included in the study regardless of the results for anti-HBcor. If the test results for HBsAg are negative but anti-HBcor total antibodies are detected, the patient

should undergo an additional examination. The additional examination should include the following: qualitative PCR for HBV DNA, anti-HBcor IgM, and a consultation with the Infectious Disease Specialist. The activity of liver transaminases and concentration of bilirubin in blood chemistry results should be also considered. Having considered the examinations and test results, the Sponsor will decide whether to approve such a patient for the study. If it is known that the patient had hepatitis B infection in the past, an additional examination may be performed along with the main examination (blood samples for HBsAg, anti-HBcor total, anti-HBcor-IgM and blood samples for qualitative PCR to HBV DNA are taken on the same day).

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 the 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 abnormalities are seen in ALT, AST, and total bilirubin,
- The Infectious Disease Specialist confirms 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 the inclusion of this patient.

If it is known that the patient had HCV infection in the past, an additional examination may be performed along with the main examination (blood samples for anti-HCV and blood samples for qualitative PCR for HCV RNA are taken on the same day).

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

[redacted]

[redacted]

The tests are performed at screening. Test results for HIV, HCV, HBV, and syphilis obtained within 1 month before signing the ICF are valid at screening.

4.7.4.5. Urinalysis

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

One urine re-testing can be performed during the screening.

4.7.5. ECG

12-lead ECG is recorded using a commonly used procedure.

4.7.6. Tuberculosis diagnostics

This study will accept results of the Diaskintest or QuantiFERON or T-spot assays obtained with standard procedures. Diaskintest/QuantiFERON/T-spot tests and their interpretations must be performed by a certified healthcare professional.

Blood assay (QuantiFERON/T-Spot) can be performed the second time if the first one (QuantiFERON/T-Spot/Diaskintest) gives uncertain/positive results, or the results of the first test cannot be interpreted because the biomaterial was spoiled, pre-analytical step was violated, or expired kits were used. No letter from the Sponsor is required.

Diagnostics of tuberculosis at screening

QuantiFERON/T-spot can be repeated once at screening. Patients with uncertain Diaskintest/QuantiFERON/T-spot 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 3 months before signing the ICF reveals no signs of active TB infection.

Diagnostics of tuberculosis at subsequent visits

In sufficient time in advance before Visits 14, 22, 25, 27, 29, 32, and 32-2, on which the test is planned (if Diaskintest is planned for the patient), the patient will receive a referral to Diaskintest. Diaskintest results should be obtained not earlier than 14 days before Visits 14, 22, 25, 27, 29, 32, and 32-2, respectively, where the test is to be performed. The Diaskintest must be performed within 7 days after the referral.

During the main and extension periods (at Visits 14, 22, 25, 27, 29, 32, and 32-2), if the first test for TB (QuantiFERON/T-spot/Diaskintest) is uncertain/positive, blood for the second test for TB (QuantiFERON or T-spot) should be drawn as soon as possible. A written approval from the Sponsor is not required. All patients with initial uncertain/positive tests for TB should undergo chest X-ray; if necessary, X-ray can be replaced with or supplemented by chest computed tomography (if lesions suggesting tuberculosis have been detected in this area).

If repeated tests (QuantiFERON/T-spot) give uncertain/positive results, the patient should be referred to a TB Specialist for a consultation. The TB Specialist should exclude or confirm the diagnosis of tuberculosis and decide whether the patient has contraindications to treatment with genetically engineered biological products (for diagnostics at Visits 14, 22, 25, 27, and 29).

Results of additional diagnostics (repeated QuantiFERON/T-spot test) should be interpreted in the following way:

If the test is negative, the patient can continue to participate in the study provided that chest X-ray shows no signs suggesting tuberculosis.

If the test is uncertain, the patient can continue to participate in the study if the TB Specialist in his/her report states that the patient has no active tuberculosis and contraindications to genetically engineered biologic drugs. At the discretion of the TB Specialist, the patient can be administered with anti-TB agents (for prophylaxis). Information about these drugs should be recorded in the TB Specialist report, other source documents (medical case history, etc.) and eCRF. If the test is positive, the AE “positive test for tuberculosis” should be recorded. If the TB Specialist in his/her record states that the patient has active tuberculosis, the patient should be withdrawn from the study and referred to the TB Specialist for further treatment. If tuberculosis is confirmed, the AE’s name should be corrected to “confirmed tuberculosis” with localization of the lesion (if

this information is available). For diagnostics at Visits 14, 22, 25, 27, and 29: if the TB Specialist states that the patient with the positive TB test result has no active tuberculosis and contraindications to biologic drugs, the patient can be administered anti-TB agents for prophylaxis, and the Sponsor should approve via a letter the continuation of the study by this patient.

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 *Mycobacterium tuberculosis* and *Mycobacterium bovis*, virulent strains of mycobacteria. The procedure and results assessment of Diaskintest® 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 occur.
- Uncertain: hyperemia with no infiltrate.
- Positive: an infiltrate (papula) of any size.

The Diaskintest® is performed at a local TB clinic or at the study site if a qualified healthcare professional is available (materials for the tests performed at study sites will be provided by JSC BIOCAD).

The Diaskintest results are valid if the test was performed within 3 months before signing the ICF. There is a high risk of false-negative results if the skin test if done more often than once in 3 months.

4.7.6.2. Plasma test for gamma interferon (QuantiFERON test)

The QuantiFERON test allows evaluating plasma levels of the specific gamma interferon to confirm or exclude the tuberculosis infection.

[redacted]

[redacted]

4.7.6.3. T-spot assay

The T-spot is an immunobiological diagnostic test for tuberculosis. It is based on counting the T cells that have been specifically activated by *Mycobacterium tuberculosis*. This test is very much like QuantiFERON assay. However, blood is collected only to one tube.

The patient must be fasting before providing a blood sample for the test. [redacted]

4.7.7. Chest x-ray

Chest X-ray is performed with standard procedures of the study site to exclude pulmonary tuberculosis or other lung diseases. The scanning is performed according to the standards of the

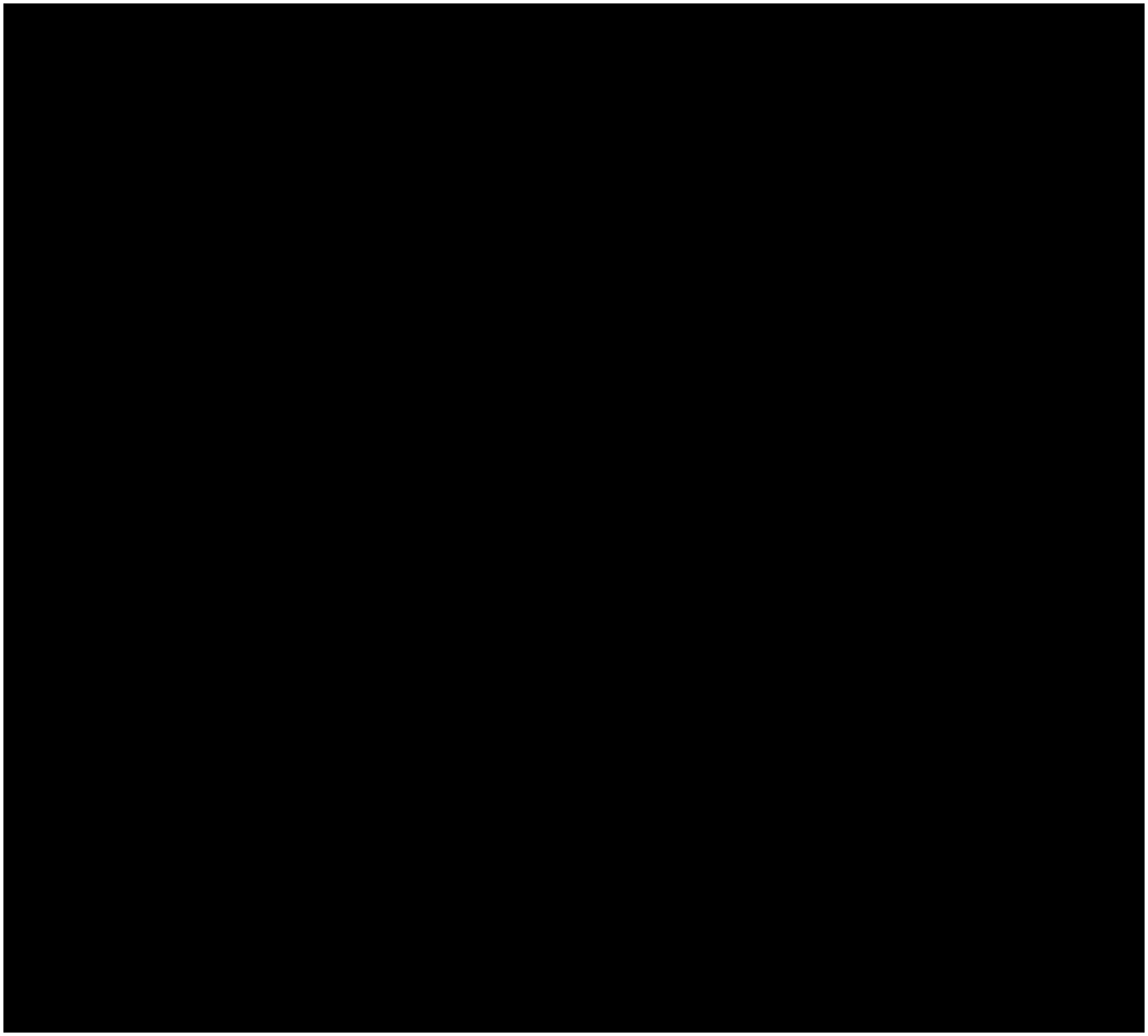
study site or third-party contractors. If necessary, the Sponsor's representative may request the images (if the subject develops active TB while in the study).

Upon reconciliation with the Sponsor, chest fluorography at screening 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 3 months before signing the ICF.

At Visits 22 (Week 54), 25 (Week 86), 27 (Week 110), 29 (Week 134), 32 (Week 158) and 32-2 (Week 170), chest X-ray should be performed only in patients with positive/uncertain results of skin or cell tests for tuberculosis. If necessary, X-ray can be replaced with or supplemented by chest computed tomography (if lesions suggesting tuberculosis have been detected in this area).

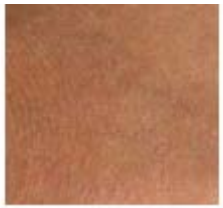
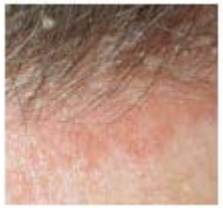
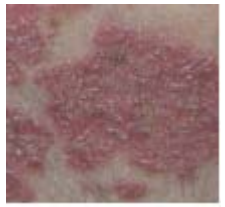
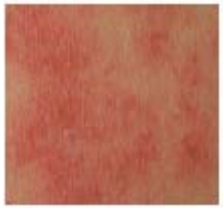
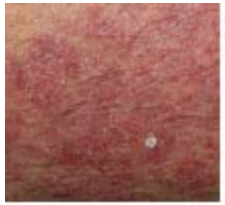
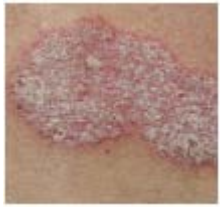
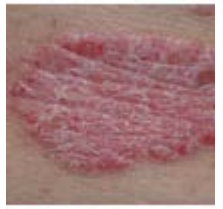
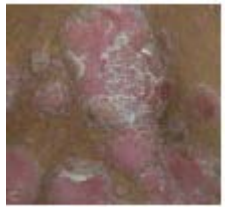
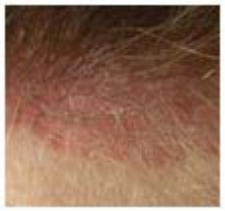
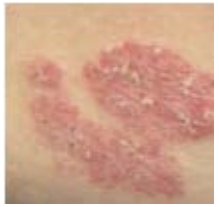
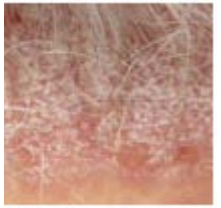
4.7.8. Assessment of the severity and area of psoriasis (PASI), including body surface area affected by psoriasis (BSA)

The area and severity of skin signs of psoriasis can be assessed with **PASI** (Psoriasis Area and Severity Index). Changes in PASI during the study are assessed vs. values at baseline (for example, PASI 75 is a reduction of the PASI score by 75% vs. baseline). [redacted]



Each symptom (erythema, infiltration, scaling) is assessed with a 4-score scale – from 0 (none) to 4 (maximum), separately for skin of head and neck, body, upper and lower extremities (lines 1-3). Assessment is performed for the area most affected by the evaluated 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
Infiltration					
Score	0	1	2	3	4
Scaling					
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 reflects about 1% of the total skin area.

To calculate *the affected area (%)*, the number of palms (from column 1 of Table 32) should be multiplied by the value from column 2 of Table 32 (one palm (%) of this body region). Thus, one palm makes up 10% of the scalp skin, 3.3% of trunk skin, 5% of the skin of the upper limbs, and 2.5% of the skin of the lower limbs.

1 palm amounts to **10%** of the head area:

% scalp psoriasis = (number of palms of scalp psoriasis) × 10%

1 palm amounts to **3.3%** of the trunk:

% trunk psoriasis = (number of palms of trunk psoriasis) × 3.3%

1 palm amounts to **5%** of the arm area:

% arm psoriasis = (number of palms of arm psoriasis) × 5%

1 palm amounts to **2.5%** of the leg area:

% leg psoriasis = (number of palms of leg psoriasis) × 2.5%

To estimate the BSA score for each section, the *affected area (%)* from each section is matched to the values from line 5 in Table 31, and the score is entered to line 6.

[redacted]

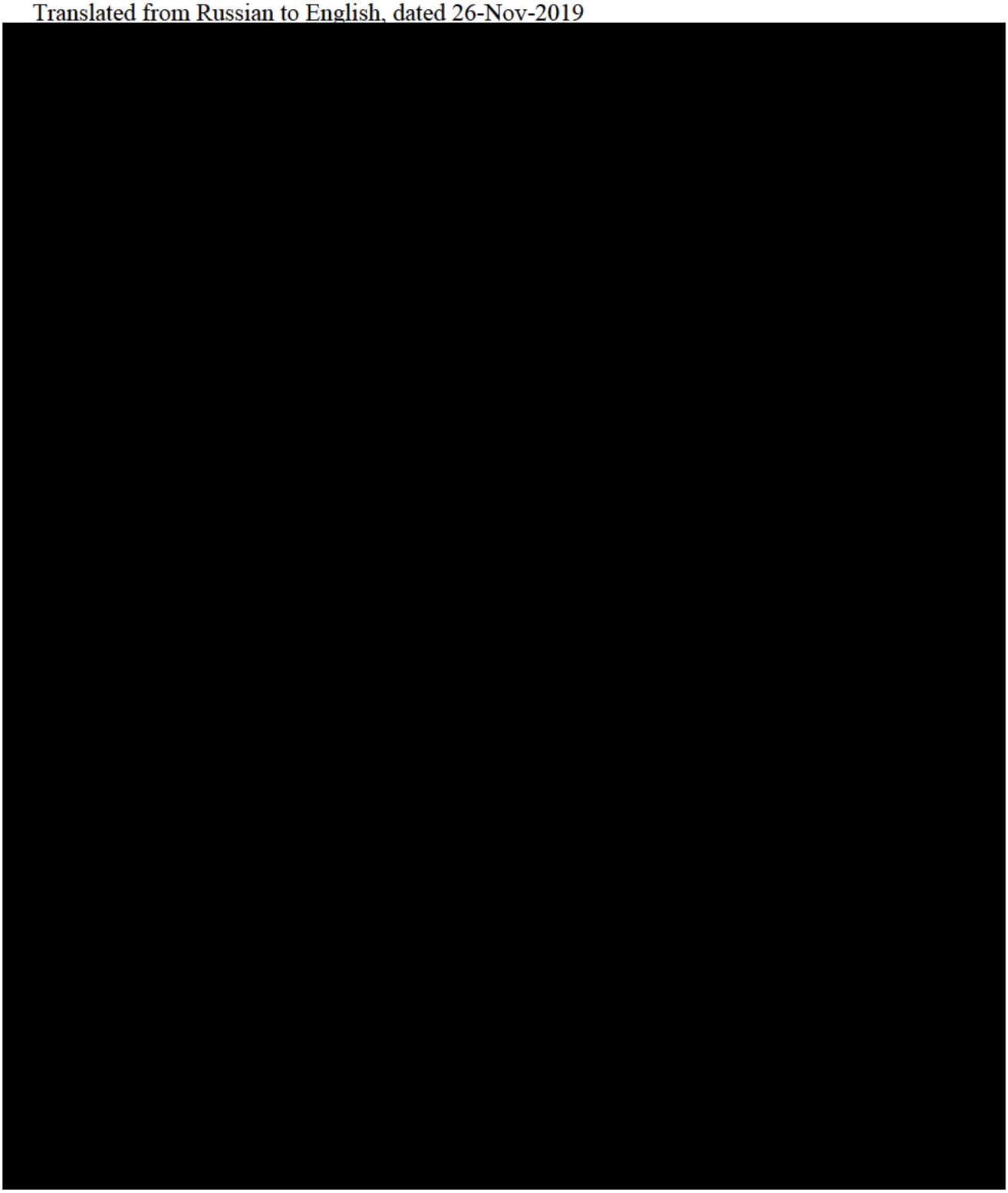
The PASI score was calculated automatically when the investigator entered the following data in the eCRF: severity of erythema, induration, and scaling by sections and the BSA. The total PASI score and severity degree of individual symptoms of several localization (lines 1-4 of Table 31) must be recorded in the source documents.

To avoid errors in PASI assessment, it is important that PASI assessment for each patient was performed by the same investigator across all visits. If necessary, the assessing investigator can be replaced once.

4.7.9. Static Physician's Global Assessment (sPGA)

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 given in Table 33 (infiltration, scaling, and erythema). Not all three criteria may be present. Infiltration is considered the most resistant symptom, while the presence of scaling or erythema can vary.

[redacted]



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

4.7.10. Quality of life assessment

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

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

Each question is assessed with a 3-score system: very much – score 3, a lot – score 2, a little – score 1, not at all or not relevant – score 0. 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 index is calculated as a sum of all scores: the minimum value is 0, the maximum – 30. The higher the score is, the more quality of life is impaired.

The survey must be filled in only by the patient or his/her legal representative. The DLQI survey must not be given to patients for completing at home. The patients should fill the questionnaire at the study site on the visit day. Completed questionnaires should be stored in the Investigator's File. The total score is calculated automatically in the eCRF after the data are entered.

4.7.11. Nail Psoriasis Severity Index (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 most affected nail is divided into quadrants. In each quadrant, the severity of the 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.

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 nail psoriasis must be assessed only in those patients who had it at screening.

4.7.12. Patient assessment of itch

The patient will assess the itch severity with a visual analog scale ranging from 0 (no itch) to 100 mm (unbearable itch).

The investigator asks the patient to mark the scale (to cross the line that corresponds to the maximum severity of experienced itching). Then the physician measures the distance (mm) from the left end of the scale (0 mm) to the patient's mark and records the result (mm).

It is required that the patient fills the scale while at the study site during the visit. The completed VAS should be stored in the Investigator's File. The score is to be recorded in the source documents. The Investigator records VAS results in the eCRF. A template of VAS is presented in Appendix 2.

4.7.13. Assessment of psoriatic arthritis

Psoriatic arthritis must be assessed only in those patients who had it at screening.

The intensity of psoriatic arthritis will be assessed according to the American College of Rheumatology Criteria (ACR20/50/70). The response will be assessed by estimating the 66/68 swollen/tender joint count, functional activity (HAQ-DI), disease activity (assessed by the physician and by the patient), patient assessment of pain (VAS), and markers of inflammation (CRP and ESR).

The ACR20 response is recorded if the patient has a 20% decrease in tender/swollen joint counts (of 68/66, respectively) and a 20% improvement in 3 (or more) of 5 parameters: VAS score (pain assessed by the patient); VAS score (activity assessed by the patient); VAS (activity assessed by the Investigator); HAQ score; ESR or CRP.

Joints are assessed by the Assessing Physician (an Investigator who underwent training on assessing joints provided by the Sponsor). During the study, the patient's joints will be assessed by one physician or, if absent, his/her representative.

Full assessment of joints

The course of psoriatic arthritis should be assessed with tender/swollen joint counts (68/66).

Physician's and patient's assessment of the disease activity and patient's assessment of pain are performed using the visual analog scales (VAS). The scales developed for this study have no gradings. The patient/physician should assess the item at his/her own discretion without using any measuring tools (ruler, etc.). It is prohibited to use the VAS for pain/disease activity that was already used at the prior visit (either for patients or for physicians). The VAS must not be given to patients for completing at home. They must be filled at the study site on the visit day. Completed VAS must be stored in the Investigator's File. The visual analogue scales are presented in Appendix 3.

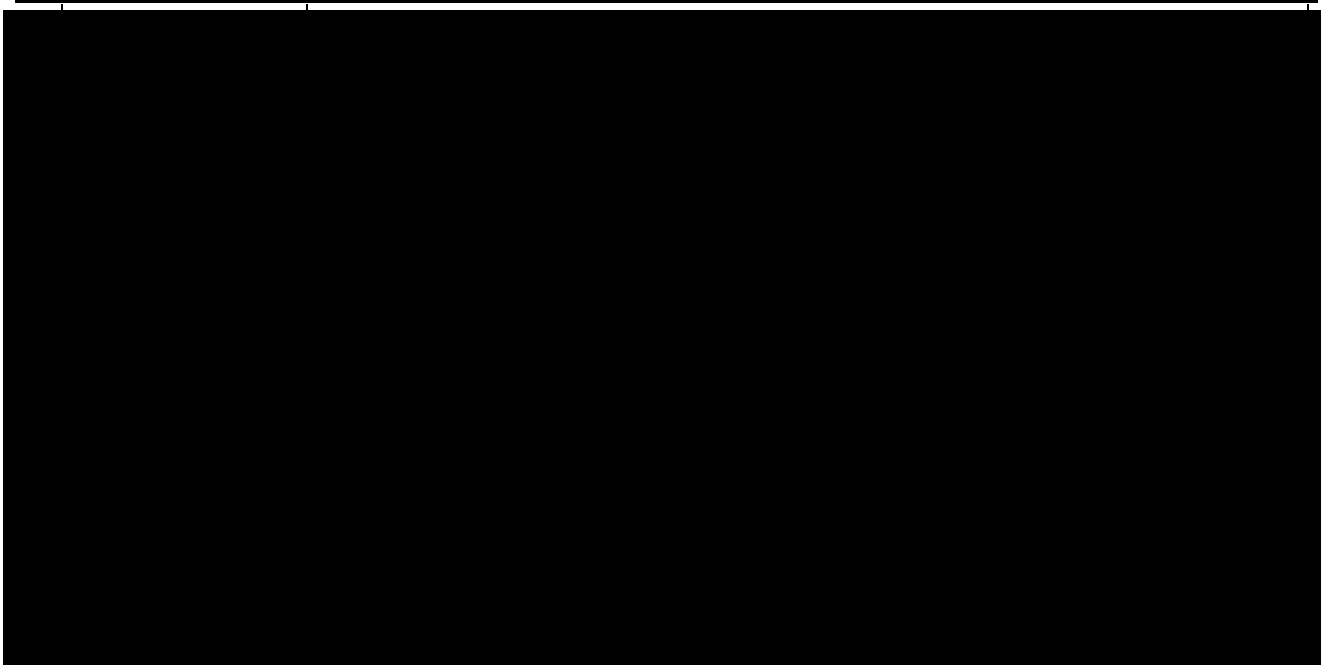
Functional ability is assessed using HAQ-DI questionnaire filled in by the patient (Annex 4). The survey must be filled in only by the patient or his/her legal representative. The HAQ-DI

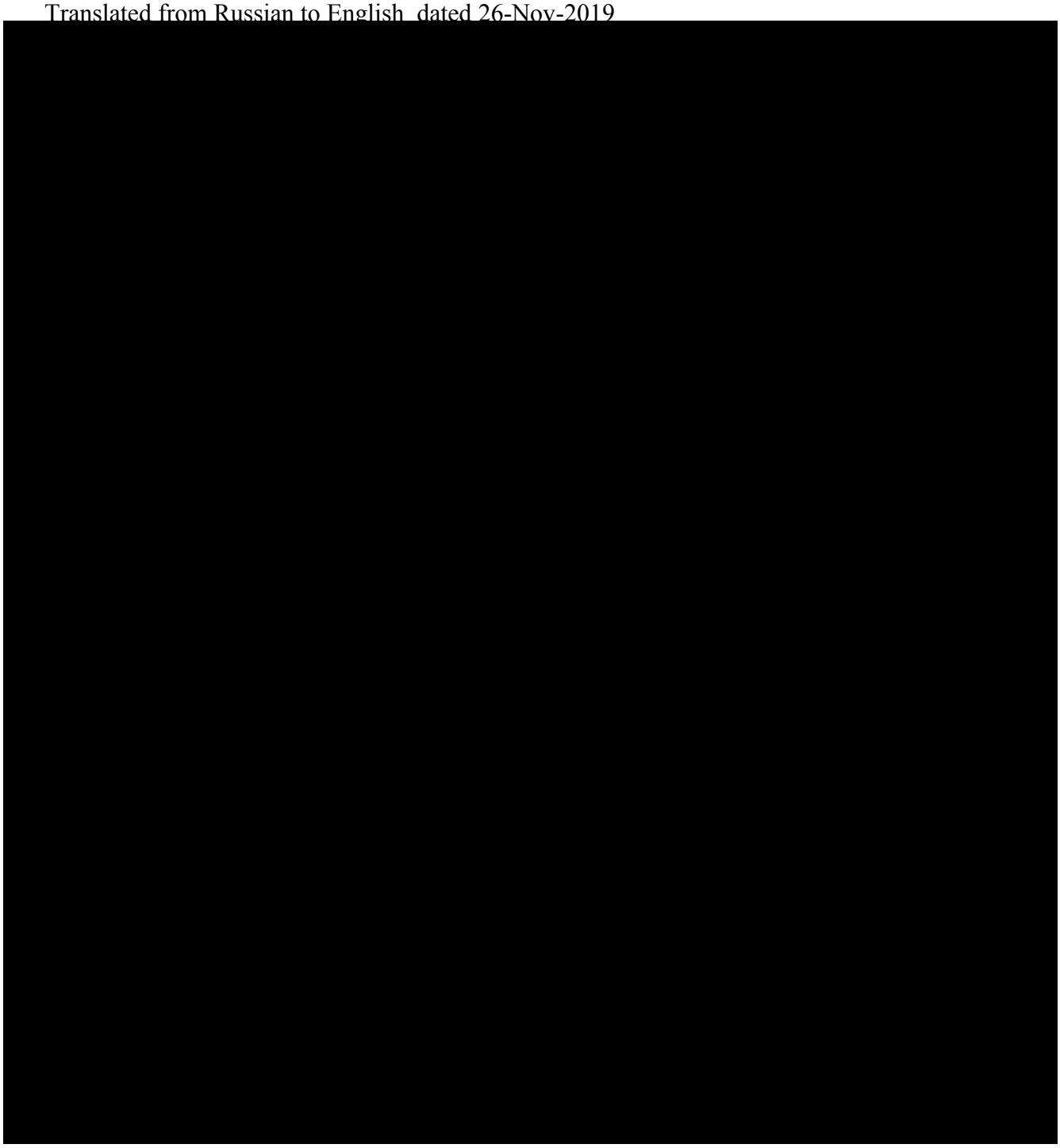
questionnaires must not be given to patients for completing at home. They must be filled in at the study site on the visit day. Completed questionnaires should be stored in the Investigator's File.

The score is calculated in automatic mode when questionnaire data are recorded in the eCRF.

4.7.14. Diagnostics of depression

This study uses Beck's Depression Inventory to evaluate depression. Beck's Depression Inventory consists of 21 groups of statements of the most common symptoms and complaints. Each group contains 4 to 5 statements referring to specific signs/symptoms of depression. Statements within one group are ranged from having the lower to the higher impact of the symptom to the overall depression severity.





Results processing:

The value of each category is calculated the following way: each item is scored from 0 to 3 depending on the increase or decrease of the symptom severity. The total Beck Inventory score is from 0 to 62 (the lower the score the better the health state).

Interpreting the Beck's Depression Inventory

Test results are interpreted as follows: 0-9 - no signs of depression; 10-15 - minimal depression (sub-depression); 16-19 - mild depression; 20-29 - moderate depression; 30-63 - severe depression.

The test is performed by the patient at screening and Visit 22 (Week 54).

Patients who scored 16 and more in the Beck's Depression Inventory are not included in the study.

4.7.15. Blood drawing for immunogenicity testing

Immunogenicity will be assessed by detecting binding and neutralizing antibodies in patients' serum. The test for binding antibodies to BCD-085 will be conducted at the Central Laboratory (JSC BIOCAD's Separate Subdivision) with validated ELISA procedures. The assay for neutralizing antibodies to BCD-085 will be performed only if the test for binding antibodies shows positive results. The neutralizing Abs assay will be done at the Central Laboratory (JSC BIOCAD's Separate Subdivision) with a validated ELISA protocol.

[redacted]

Do not use hemolyzed (bright red) or lipemic (milk-white) serum specimens, or serum specimens with a sediment after spinning.

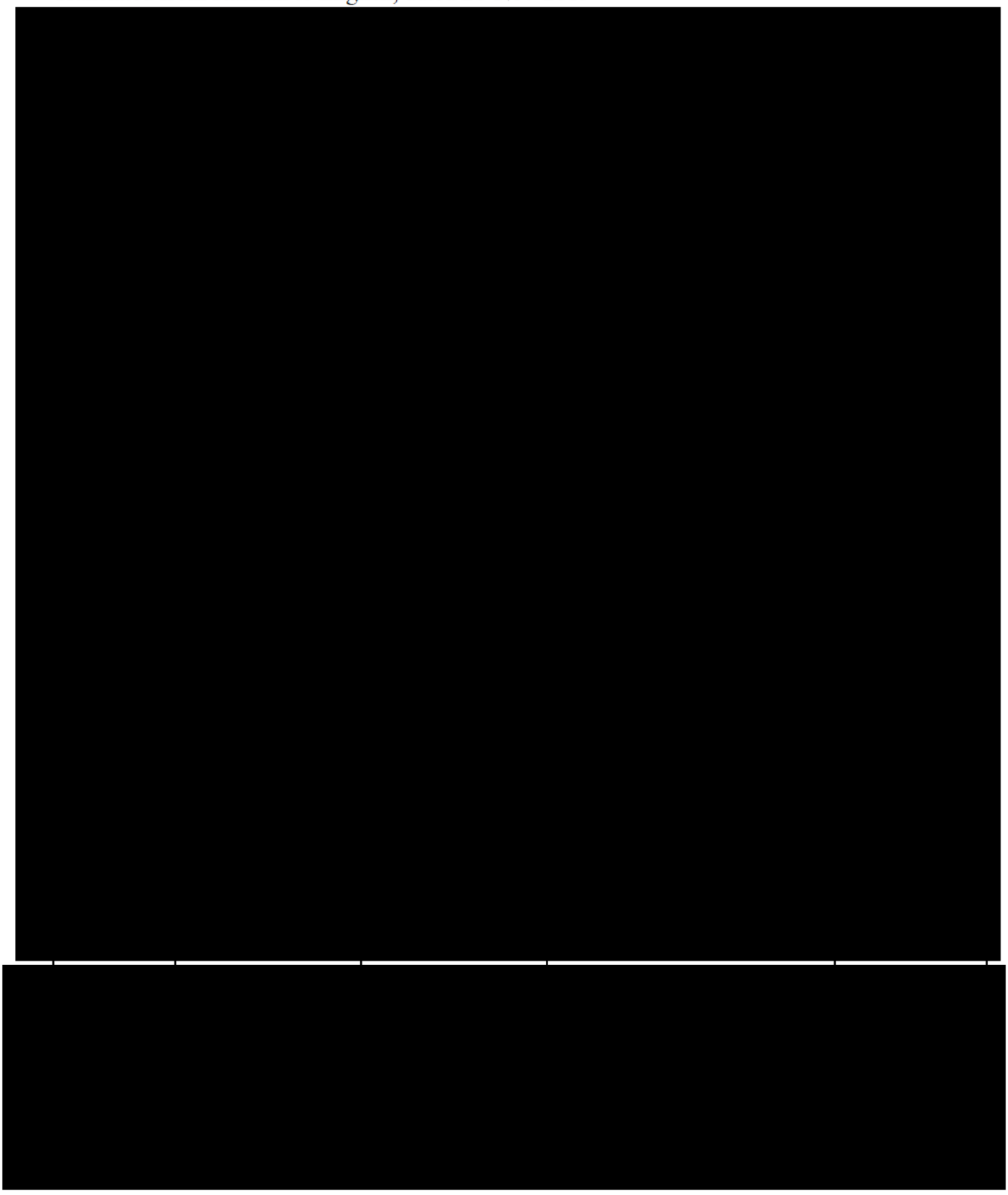
[redacted]

A courier service authorized by JSC BIOCAD will deliver samples to the central lab, maintaining the temperature regimen (on dry ice).

After the study closeout, the retained samples may be destroyed according to the study site's SOPs.

The first blood sample will be taken on Visit 1 before the injection of the investigational product. Starting from Week 64, time points for blood drawing for immunogenicity testing will differ between patients from Arms 1/2 and 3. Therefore, during the extension study period, the label will also contain study week number (for example, IG4-1A64).

[redacted]



4.7.16. Storage and shipping of biospecimens

Serum specimens should be stored at the study site until they are shipped to the central laboratory. Specimens will be shipped to the central lab by batches after patients assigned to this

study site provide all blood samples specified by the Protocol and the CRA checks the availability of all required samples during the routine monitoring visit. [redacted] All shipments to the central laboratory will be made via a delivery service. Contact information of the courier company and central laboratory will be provided by the study CRA.

Before shipping the specimens, the member of the study team should notify the analytical laboratory staff and agree upon the shipping date by phone.

4.7.17. Total blood volume taken during the study

Table 39 gives the estimated volume of blood to be taken at each visit and during the entire study.

Table 39. 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	[redacted]	[redacted]

[98] TB diagnostics can be performed with the skin test (Diaskintest) or blood test (QuantiFERON/T-spot). [redacted]

Visit	Laboratory tests (frequency / blood taken per 1 sample)	Total blood volume
	[redacted]	
Visit 1 (Day 1 of Week 0)	[redacted]	[redacted]
Visit 6 (Day 1 of Week 8)	[redacted]	[redacted]
Visit 8 (Day 1 of Week 12)	[redacted]	[redacted]
Visit 13 (Day 1 of Week 24)	[redacted]	[redacted]
Visit 14 (Day 1 of Week 26)	[redacted]	[redacted]
Visit 16 (Day 1 of Week 34)	[redacted]	[redacted]
Visit 18 (Day 1 of Week 42)	[redacted]	[redacted]
Visit 21 (Day 1 of Week 52)	[redacted]	[redacted]
Visit 22 (Day 1 of Week 54)	[redacted]	[redacted]

[redacted]

Visit	Laboratory tests (frequency / blood taken per 1 sample)	Total blood volume
Visit 23 (Day 1 of Week 62)	[redacted]	[redacted]
Visit 23-1[100] (Day 1 of Week 64)	[redacted]	[redacted]
Visit 24 (Day 1 of Week 74)	[redacted]	[redacted]
Visit 25 (Day 1 of Week 86)	[redacted]	[redacted]
Visit 26 (Day 1 of Week 98)	[redacted]	[redacted]
Visit 27 (Day 1 of Week 110)	[redacted]	[redacted]
Visit 28 (Day 1 of Week 122)	[redacted]	[redacted]

[100] Visits 23-1, 32-1, 32-2 are performed only in patients from Arm 3.
[101] Only for patients from Arms 1 and 2.
[redacted]
[103] Only for patients from Arm 3.
[redacted]

Visit	Laboratory tests (frequency / blood taken per 1 sample)	Total blood volume
	[redacted]	
Visit 29 (Day 1 of Week 134)	[redacted]	[redacted]
Visit 30 (Day 1 of Week 146)	[redacted]	[redacted]
Visit 31 (Day 1 of Week 154)	[redacted]	[redacted]
Visit 32[108] (Day 1 of Week 158)	[redacted]	[redacted]
Visit 32-1[110] (Day 1 of Week 166)	[redacted]	[redacted]
Visit 32-2[110] (Day 1 of Week 170)	[redacted]	[redacted]

[105] Only for patients from Arm 3.
[106] Only for patients from Arms 1 and 2.
[107] TB diagnostics can be performed with the skin test (Diaskintest) or blood test (QuantiFERON/T-spot).
[108] Visit 32 is performed only in patients from Arms 1 and 2.
[109] TB diagnostics can be performed with the skin test (Diaskintest) or blood test (QuantiFERON/T-spot).
[110] Visits 23-1, 32-1, 32-2 are performed only in patients from Arm 3.

Visit	Laboratory tests (frequency / blood taken per 1 sample)	Total blood volume
	[redacted]	
Total blood volume drawn from one subject over the entire study		**For Arms 1 and 2: approximately 392 mL** **For Arm 3: approximately 429 mL**[111]

[redacted]

[111] If re-tests or additional tests are required, the total blood volume will not exceed 457 mL (for Arms 1 and 2) or 494 mL (for Arm 3).

[redacted]

[redacted]

4.7.19. Assessment of the Patient's Diary

The Patient' Diary is dispensed at Visit 22 (Day 1 of Week 54) and covers the whole extension study period.

The Investigator records in the Diary the contact details of the study site and the date of the next visit. The patient should be asked to document all injections in the Diary. If the patient has missed an injection, he/she should record this together with the reason. The patient should record all information about his/her health, including adverse events and their dynamics, and all medications he/she takes (study and concomitant therapies).

The Patient's Diary is checked and taken back at all scheduled visits. Pages withdrawn from the Patient's Diary should be kept as source documents.

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.

The eCRF 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 Patient IDs. Screening ID can only be used until the patient is randomized in the study. After randomization, screening IDs must be changed to Patient IDs.

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. JSC BIOCAD decides to stop the study due to safety reasons, ethical considerations,

compliance issues, or any other reasons.

2. Local ethics committees or regulatory authorities decide to stop the study.

4.8.2. Criteria for premature withdrawal of study subjects

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

1. Major violations of inclusion and/or exclusion criteria revealed after the enrollment (patients removed at the discretion of JSC BIOCAD)[112].
2. The patient withdraws his/her consent to participate in the study.
3. The patient develops AEs or SAEs (including depressions), 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. During the main treatment period: The patient misses more than 2 injections (in this case, the patient's removal must be approved by JSC BIOCAD, refer to section 6.3.1. *Treatment compliance*) or misses 2 consecutive visits or 3 visits in total, or the patient regularly (7 times or more) violates the timing of the scheduled visits.
5. During the extension treatment period (Week 54 to Week 154 for patients from Arms 1 and 2, Week 54 to Week 166 for patients from Arm 3): if ≥ 20% injections are missed (≥ 5 injections for patients initially randomized in Arms 1 or 2, ≥ 6 injections for patients initially randomized in Arm 3) or ≥ 2 consecutive visits/injections are missed;
6. The patient gets pregnant. If pregnancy is suspected, the urine test for HCG must be performed. If the test gives a positive result, the patient must be withdrawn from the study (follow-up procedures are described in section 5.4).
7. The patient is diagnosed with active tuberculosis during the treatment with the investigational product (the diagnosis should be confirmed by a documented impression from the TB Specialist);
8. The study is terminated by the decision of JSC BIOCAD, local ethics committees or regulatory authorities.
9. The patient uses medications prohibited by the Protocol.
10. The patient dies.

[112] Violation of eligibility criteria justified by the investigator and approved by the Sponsor is not a reason for removing the patient from the study.

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

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

Patients who discontinue the study will not be replaced.

For further details see Section 11.6. *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.

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.

Drug accountability records must be available to the CRA during each monitoring visit.

Accounting records should include:

- Delivery confirmation;
- Inventory at the study site;
- Use of the investigational products 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 provided by JSC BIOCAD; Unused investigational product is not used for any other purpose except this study.

  The CRA from JSC BIOCAD will regularly inspect drug accountability records.

The patient will return used syringes in a special container and cardboard cartons (secondary packaging) at every visit. The investigator should check the amount of the investigational product used.

4.9.1. Handling of the investigational products

The investigational product will be delivered to the study site before the study start (before the inclusion of the first patient). All packs will have a "For clinical studies" label.

At the study site, the investigational product must be stored at 2 to 8 °C, protected from light, in a limited access area. Access to the storage area will be granted only to the Principal Investigator, co-investigators, members of the study team, and an authorized representative of the site administration who has access to the storage area granted by the local regulations. The investigator must maintain a temperature log.

The investigator must ensure safe storage of the investigational product to prevent loss, theft, or improper environmental conditions (temperature) specified by the Sponsor and described in the Investigator Brochure.

During the extension period from Week 54, BCD-085 will be given to the patients so that they can self-inject it at home. The investigational product should be transported by the patients in a cooling bag with additional cold packs to keep the temperature mode. The investigators should inform the patients that after arriving at home they should place the investigational product in the refrigerator (not in the freezer) at 2 to 8 °C; the investigational product must not be frozen. Guidelines on transportation, storage and use of the investigational product are given in the Patient's Diary. Patients should be informed that they have to return a container with used syringes and cardboard cartons of the secondary packaging back to the study site during each visit. If there is no injection scheduled, the patient should return unused syringes. The investigator should check the amount of the investigational product used (and not used, if applicable).

4.10. Procedure for code keeping and unblinding

As this study is double-blind, the test product and placebo will be identified only by the patient-specific lot number. JSC BIOCAD will prepare 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 site 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.

The 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. 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. In emergency cases, when urgent unblinding is required for the patient's benefit, the Investigator can unblind the treatment code first and then inform the representative of the Sponsor. After completing all necessary procedures, the Investigator should fill out the unblinding form and send it to JSC BIOCAD (to the Study Monitor, Drug Safety Division or Medical Expert) within 24 h from the moment when the code was unblinded. After unblinding, the Investigator should record this in the source documents.

At Week 12, the treatment will be unblinded by opening the randomization envelops. This should be recorded in the primary documentation.

Each patient participating in the study will receive a Study Subject's Card, which will contain the Protocol title and code, study site number, and contact data of the Investigator. 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 healthcare professional of another medical facility (other than the study center) can contact the Investigator to discuss benefits 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 to be recorded in the CRF should be present in the source documents of the study site.

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 (ICF).
2. Age of at least 18 years old at the time of signing the ICF.
3. Moderate to severe plaque psoriasis diagnosed at least 6 months before signing the ICF.
4. Patients who received at least one course of phototherapy or [113] systemic therapy for psoriasis or are candidates[114] for such treatment according to the investigator.
5. Body surface area (BSA) affected by psoriasis of 10% or greater, the PASI score of 10 or greater, and the sPGA score of 3 or greater at screening.
6. 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).
7. The ability of the patient (in the Investigator's opinion) to follow the Protocol procedures.
8. Patients of both sexes and their partners with reproductive potential must implement reliable contraceptive methods starting from signing the ICF to 20 weeks after the last dose of the investigational product. This requirement does not apply to patients after surgical sterilization and to females who are post-menopausal for 2 years or longer. Reliable contraceptive methods include one barrier method in combination with one of the following: spermicides, intrauterine device/oral contraceptives.

5.2. Exclusion criteria

1. Baseline erythrodermic, pustular, or guttate psoriasis or any other skin disorders (e.g. eczema) that can affect/complicate the assessment of psoriasis treatment.
2. Use of the following medications:
    - Prior exposure to any therapeutic monoclonal antibodies targeting IL-17 or its receptor;
    - Prior exposure to more than one drug containing monoclonal antibodies or their fragments;
    - Prior exposure to any monoclonal antibodies given within 12 weeks before signing the ICF;

[113] Systemic therapy refers to any non-biologics (methotrexate, cyclosporine, acitretin, mycophenolate mofetil, apremilast, calcitriol derivatives, etc.), or genetically engineered biologics (TNF inhibitors, anti-cytokine drugs, anti-CD20 drugs, etc.).
[114] BCD-085 is planned to be used as either a first- or second-line treatment, so the study involves treatment-naive patients along with those who failed to respond to systemic therapy or phototherapy.

- Use of any systemic[115] medications for the treatment of psoriasis (including glucocorticoids, methotrexate, sulfasalazine, cyclosporine, acitretin, mycophenolate mofetil, apremilast, calcitriol derivatives, etc.) within 4 weeks before signing the ICF. If these drugs were stopped less than 4 weeks before signing the ICF, the screening period should be extended up to 8 weeks during which no new systemic drugs are allowed;
- Use of phototherapy within 4 weeks before signing the ICF;
- Use of topical[116] medications for the treatment of psoriasis within 2 weeks before signing the ICF;
- Vaccination with live or attenuated vaccines within 8 weeks before signing the ICF.

3. Any active systemic infection or recurrent infection at screening/randomization.
4. HIV, hepatitis B, hepatitis C, or syphilis[117].
5. Blood chemistry abnormalities appearing as:

   a) creatinine > 2 × upper limit of normal (ULN) at screening;

   b) ALT, AST or alkaline phosphatase > 2.5 × ULN at screening;

   c) bilirubin > 1.5 × ULN at screening;

[115] Except for NSAIDs.
[116] Patients may use topical glucocorticoids (of mild to moderate potency) on the face, underarm, and genitals. Patients may also use topical moisturizers, emollients, oils, and salicylic acid ointments, topical antibacterial and/or antimycotic agents as needed. Patients should discontinue all local skin products (medications or cosmetics) 24 hours before the planned PASI assessment.
[117] The screening for HBV includes tests for HBsAg and total antibodies to HBcor antigen (anti-HBcor total = IgG + IgM). If the test results for these markers (HBsAg and anti-HBcor total) are negative, the patient is considered eligible for the study by this criterion. If the patient tests positive for HBsAg, the patient cannot be included in the study regardless of the results for anti-HBcor. If the test results for HBsAg are negative but anti-HBcor total antibodies are detected, the patient should undergo an additional examination. The additional examination should include the following: qualitative PCR for HBV DNA, anti-HBcor IgM, and a consultation with the Infectious Disease Specialist. The activity of liver transaminases and concentration of bilirubin in blood chemistry results should be also considered. Having considered the examinations and test results, the Sponsor will decide whether to approve such a patient for the study. If it is known that the patient had hepatitis B infection in the past, an additional examination may be performed along with the main examination (blood samples for HBsAg, anti-HBcor total, anti-HBcor-IgM and blood samples for qualitative PCR to HBV DNA are taken on the same day).
The patient with anti-HCV antibodies can be included in the study if all of the following conditions are met: negative qualitative PCR results for HCV RNA (this test is performed only if anti-HCV antibodies are detected); no abnormalities (increased transaminases or bilirubin levels) found in blood chemistry; the Infectious Disease Specialist provides a documented conclusion that the patient has no HCV/cured HCV; and the Sponsor approves the enrollment of this patient. If it is known that the patient had HCV infection in the past, an additional examination may be performed along with the main examination (blood samples for anti-HCV and blood samples for qualitative PCR for HCV RNA are taken on the same day).
The patient who has a positive test for syphilis can be included in the study at the discretion of the Sponsor if the Dermatology/Venereology Specialist provides a documented report that the patient has no syphilis/cured syphilis. An additional examination may be required to confirm the diagnosis (at the discretion of the Dermatology/Venereology Specialist).

6. Leukocyte count < 3.0 × 10^9/L; absolute neutrophil count < 2.0 × 10^9/L; platelet count < 100 × 10^9/L, or hemoglobin < 90 g/L according to complete blood count at screening.
7. Any psychiatric conditions including severe depressive disorders and/or any history of suicidal thoughts or suicidal attempts[118].
8. Signs of clinically significant depression (Beck's score ≥ 16 at screening).
9. Alcohol or substance abuse.
10. Tuberculosis now or in the past.
11. Latent TB infection (positive results of the Diaskintest[119], QuantiFERON test, or T-spot).
12. Confirmed by source documentation and ongoing at screening, concurrent diseases that may increase the risk of adverse events during the study therapy or affect the evaluation of psoriasis symptoms (mask, enhance or alter the symptoms of psoriasis, or cause clinical or laboratory/instrumental symptoms similar to those of psoriasis):
    - Active inflammatory diseases or aggravation of chronic inflammatory diseases other than psoriasis;
    - Functional class III-IV stable angina of effort, unstable angina or a history of myocardial infarction within 1 year before signing the ICF;
    - Moderate to severe cardiac failure (NYHA class III-IV);
    - Treatment-resistant hypertension[120];
    - Severe asthma, a history of angioedema;
    - Moderate to severe respiratory failure, grade 3/4 chronic obstructive pulmonary disease;
    - Diabetes mellitus with inadequate glycemic control, i.e. if HbA1C[121] level is ≥ 8% (to be valid, results should be obtained at screening or within 3 months before signing the ICF);

[118] This exclusion criterion can be confirmed or rejected on the basis of medical records or as told by the patient. Patient's medical history that can, in the opinion of the investigator, jeopardize the patient or affect his/her ability to follow the protocol must be carefully evaluated.
[119] TB diagnostics can be performed with the skin test (Diaskintest) or blood test (QuantiFERON/T-spot). QuantiFERON/T-spot can be repeated once. Upon reconciliation with the Sponsor, the patient with uncertain Diaskintest/QuantiFERON/T-spot results can be enrolled in the study if the TB Specialist confirms in written that the patient has no TB infection, and the patient shows no signs of active TB according to the chest X-ray performed any time within 3 months before signing the ICF or during the screening. The Diaskintest results are valid if the test was performed within 3 months before signing the ICF.
[120] Treatment-resistant arterial hypertension is defined as blood pressure above the target range despite the concurrent use of a combination of three anti-hypertensive drugs of different classes, necessarily including a diuretic, and non-medication methods (salt-free diet, controlled physical exercise).
[121] Glycated hemoglobin is measured only in patients with suspected/diagnosed diabetes mellitus.

- Thyrotoxicosis persisting despite thyrostatic drugs or hypothyroidism not compensated with thyroid hormone drugs[122];
- Systemic autoimmune diseases (including but not limited to systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, non-specific ulcerative colitis, systemic scleroderma, inflammatory myopathy, mixed connective tissue disease[123], overlap syndrome, etc.);
- Any other underlying conditions (including but not limited to metabolism, hematology, renal, hepatic, pulmonary, neurological, endocrine, cardiac, and gastrointestinal disorders; infections) that, in the opinion of the Investigator, may affect the course of psoriasis, affect the assessment of its symptoms, or put the patient using the study therapy at unacceptable risk.

13. Malignancies with less than 5 years of remission.
14. Known severe allergies (anaphylaxis or drug allergy to two or more drugs).
15. Known allergy or intolerance to monoclonal antibody drugs (murine, chimeric, humanized, or fully human) or any other components of the test drug or comparator.
16. Major surgery within 30 days before the screening, or a major surgery being scheduled at any time during the study.
17. Severe infections (including those that required hospitalization or parenteral antibacterial/antimycotic/antiprotozoal agents) within 6 months before signing the ICF.
18. Use of systemic antibacterial/antimycotic/antiprotozoal agents within 2 months before signing the ICF.
19. More than 4 episodes of respiratory infections within 6 months before signing the ICF.
20. Episodes of systemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis, etc.) within 6 months before signing the ICF.
21. History of epileptic attacks or seizures.
22. Any concurrent diseases during which, in the Investigator's opinion, the study therapy can harm the patient.
23. Pregnancy, breastfeeding, or planning for pregnancy while participating in the study.

[122] In case of a history of thyroid disorders with thyrotoxicosis or hypothyroidism, the patient can participate in the study if he/she has laboratory confirmation of euthyroidism within 3 months before signing the ICF, and no symptoms developing during therapy with stable doses of antithyroid drugs/thyroid hormones for at least 4 weeks before signing the ICF.
[123] Signs/symptoms of psoriatic arthritis are not considered an exclusion criterion.

24. Participation in any other clinical study within 3 months before signing the ICF or simultaneous participation in other clinical studies.
25. Patients who have been already randomized in the study but then withdrawn due to any reasons cannot be included in the study.

5.3. Withdrawal criteria

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

1. Major violations of inclusion and/or exclusion criteria revealed after the enrollment (patients removed at the discretion of JSC BIOCAD)[124].
2. The patient withdraws 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. During the main treatment period: The patient misses more than 2 injections (in this case, the patient's removal must be approved by JSC BIOCAD, refer to section 6.3.1. *Treatment compliance*) or misses 2 consecutive visits or 3 visits in total, or the patient regularly (7 times or more) violates the timing of the scheduled visits.
5. During the extension treatment period (Week 54 to Week 154 for patients from Arms 1 and 2, Week 54 to Week 166 for patients from Arm 3): If ≥ 20% injections are missed (≥ 5 injections for patients initially randomized in Arms 1 or 2, ≥ 6 injections for patients initially randomized in Arm 3) or ≥ 2 consecutive visits/injections are missed;
6. The patient gets pregnant. If pregnancy is suspected, the urine test for HCG must be performed. If the test gives a positive result, the patient must be withdrawn from the study (follow-up procedures are described in section 5.4).
7. The patient is diagnosed with active tuberculosis during the treatment with the investigational product (the diagnosis should be confirmed by a documented impression from the TB Specialist);
8. The study is terminated by the decision of JSC BIOCAD, local ethics committees or regulatory authorities.
9. The patient uses medications prohibited by the Protocol.

[124] Violation of eligibility criteria justified by the investigator and approved by the Sponsor is not a reason for removing the patient from the study.

10. The patient dies.

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

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 the investigational product

The following should be done if the patient who received at least one dose of the investigational product discontinues the study early:

- On the day of withdrawal, the Early Withdrawal Visit should be conducted and the investigator should complete the Early Withdrawal Visit and the End of Study forms in the eCRF. The Protocol does not specify the amount of procedures to be performed during the Early Withdrawal Visit; this is to be determined on a case-by-case basis.

Said procedures are mandatory for all subjects who prematurely withdrew from the study, except for the subjects who are lost to follow-up or are physically unable to attend the visit. All records must be supported with appropriate source documents.

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 is to be **followed up until the AE or SAE resolves completely**.

If a woman involved in the clinical study or a partner of a clinical study participant becomes pregnant, this does not need to be reported as an AE unless the baby has any congenital abnormality or birth defect (these should be recorded as SAEs). However, all pregnancies must be documented in a Pregnancy Report Form and reported to the Sponsor as soon as possible. Women who discontinued the study because of becoming pregnant during the study should be monitored throughout the entire pregnancy and 6 months after childbirth to evaluate the mother's and child's health. Such monitoring is performed when possible and requires patient's consent for the pregnancy follow-up. Information on pregnancy course and outcome should be recorded in the source documentation (with consent from the patient).

Information about the health of the patient prematurely withdrawn from the study must be recorded in the source documentation and eCRF.

5.4.2. Follow-up of subjects who did not receive a single dose of the investigational product

If the patient discontinues the study before getting the first dose of the investigational product, the investigator must fill out the End of Study Form in eCRF 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 discontinues the study before the first dose of the investigational product, his/her information will not be included in the safety analysis.

6. TREATMENT OF STUDY SUBJECTS

6.1. Study therapy

In **Arm 1**, the test drug BCD-085 will be used at a dose of 120 mg given as two subcutaneous injections according to the following schedule: once a week for the first 3 weeks (induction treatment) and then once every 2 weeks through Week 10 (inclusive). After 10 weeks, patients will receive BCD-085 once every 4 weeks starting from Week 14 through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 154.

In **Arm 2**, the test drug BCD-085 will be used at a dose of 120 mg given as two subcutaneous injections according to the following schedule: once a week for the first 3 weeks (induction treatment) and then Q4W (maintenance treatment) through Week 10. Thus, the drug will be administered on Day 1 of Week 0, Day 1 of Week 1, Day 1 of Week 2 (induction therapy), Day 1 of Week 6, Day 1 of Week 10. To maintain the study blind, patients of this arm will receive placebo (2 injections) on Day 1 of Week 4 and Week 8. After 10 weeks, patients will receive BCD-085 once every 4 weeks starting from Week 14 through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 154.

In **Arm 3** (control arm), patients will receive 2 subcutaneous injections of placebo (1.0 mL each) on Day 1 of Weeks 0, 1, 2, 4, 6, 8 and 10. Patients will receive BCD-085 120 mg once a week at Weeks 12, 13, 14, then Q4W starting from Week 18 through Week 50. If achieving ≥PASI 75 response at Week 52, patients will receive treatment with BCD-085 Q4W from Week 54 through Week 166. If failing to achieve ≥ PASI 75 response at Week 52, patients will discontinue the study.

Patients will be followed up for 4 weeks after the last injection of the investigational product.

Injections can be given to the abdomen, hips, or upper arms. Injections should be given at least 5 cm apart.

Patients are not allowed to use phototherapy, systemic therapy (except for NSAIDs) or live vaccines while they are in the study.

Patients may use topical glucocorticoids (of mild to moderate potency) on the face, underarm, and genitals Patients may also use topical moisturizers, emollients, oils, and salicylic

acid ointments, topical antibacterial and/or antimycotic agents as needed. 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

Regardless of the arm where the patient is assigned to, during the main study period (Week 0 through Week 54) SC injections will be performed by an authorized member of the study team at the study site (except for the injection on Week 54).

At Week 54 patients will be trained on how to self-inject the investigational product. If necessary, the training can be repeated at any of the subsequent visits.

During the extension study period (Week 54 to Week 154 for patients from Arms 1 and 2, Week 54 to Week 166 for patients from Arm 3), patients will self-inject the investigational product at home (on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150 in Arms 1 and 2; on Day 1 of Weeks 58, 66, 70, 78, 82, 90, 94, 102, 106, 114, 118, 126, 130, 138, 142, 150, 158, 162 in Arm 3) after relevant training at the study site at Week 54. Injections of the investigational product on visit dates will be performed by an authorized member of the study team at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154 (in Arms 1 and 2) or at Weeks 62, 74, 86, 98, 110, 122, 134, 146, 154, 166 (in Arm 3). The first self-injection of the investigational product at Week 54 will be performed under the supervision of an authorized member of the study team.

At each visit from Week 54 to 146, patients will receive the investigational product for self-administration in an amount sufficient until the next visit [redacted].

[redacted]

[redacted]

Injections can be given to the abdomen, hips, or upper arms. Injections should be given at least 5 cm apart.

The investigational product should be transported by the patients in a cooling bag with additional cold packs to keep the temperature mode. The investigators should inform the patients that after arriving at home they should place the investigational product in the refrigerator (not in the freezer) at 2 to 8 °C; the investigational product must not be frozen. Guidelines on transportation, storage and use of the investigational product are given in the Informed Consent Form and the Patient's Diary. Patients should be informed that they have to return a container with used syringes and cardboard cartons of the secondary packaging back to the study site during each visit. If there is no injection scheduled, the patient should return unused syringes. The investigator should check the amount of the investigational product used (and not used, if applicable).

Procedure for subcutaneous injection:

The subcutaneous injection procedure is presented in the Patient Information Sheet with the Informed Consent Form, as well as in the Patient's Diary.

[redacted]

- [redacted]

[redacted]

Disposal of auxiliary materials

Unused solution of the investigational product, used syringes, cotton swabs, and other auxiliary materials should be disposed of according to study site procedures.

The secondary packages should be stored at the study site until the visit of the study CRA so they can be counted. After being counted, they can be disposed of.

During the extension period, patients will self-inject the investigational product at home. They should place used syringes in a special container and return it at a closest scheduled visit. The patients should also return the secondary packaging of the investigational product (cartons) to the study site so that the Clinical Study Monitor can count them.

6.1.2. Adjustment and discontinuation of study therapy

6.1.2.1. Dose modification and discontinuation of the investigational product

No dose modifications for the investigational product 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.

6.1.2.1.1. Follow-up for toxicity

In case of temporary or permanent treatment 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 the investigational product.

6.1.3. Overdose

6.1.3.1. Overdose with the test drug

No overdose events have been described with BCD-085. The effects of BCD-085 injected at single doses higher than 3 mg/kg are not known.

In this study, an overdose is defined the following way: administration of BCD-085 at a dose greater than 120 mg or shortening of the interval between two doses by more than 3 days. Shortening the between-visit periods by 3 days or less is not considered an overdose.

If an overdose is registered in this study, and the patient develops some adverse symptoms 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 may use topical glucocorticoids (of mild to moderate potency) on the face, underarm, and genitals. The patients may use topical moisturizers, emollients, oils, or salicylic acid ointments as needed. Patients should discontinue all local skin products (medications or cosmetics) 24 hours before the planned PASI assessment.

The patients can use single doses of systemic glucocorticoids to manage acute anaphylactic reactions, shock, or other life-threatening events that have developed as adverse events during the study.

The patients can use non-steroidal anti-inflammatory drugs (NSAIDs) and medications for the treatment of other disorders (except for psoriatic arthritis).

6.2.2. Prohibited concomitant therapy

Methods and medications prohibited in this study:

- ✓ Biologics (including other anti-IL-17 monoclonal antibodies, TNFα inhibitors, anti-cytokine agents, etc.);

- ✓ Systemic medications for psoriasis/psoriatic arthritis, including hydroxyurea, acitretin, cyclosporine, methotrexate, apremilast, fumaric acid derivatives and dimethyl fumarate, intracellular kinase inhibitors, etc., except for NSAIDs;
- ✓ Systemic and intra-articular glucocorticoids;
- ✓ Phototherapy [including selective phototherapy (UVB) and photochemotherapy (PUVA)],
- ✓ Any unauthorized products other than BCD-085;
- ✓ Opioid analgesics;
- ✓ Vaccination with live vaccines.

The study participant who has 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.

6.3.1. Treatment compliance

Criteria of treatment non-compliance during the period from Week 0 to Week 52 (the patient must be withdrawn from the study if meeting any of them):

- The patient misses more than 2 injections of the investigational product (removal should be reconciled with JSC BIOCAD), or

- The patient misses 2 consecutive visits or a total of 3 visits in the study, or

- The patient regularly violates the visit schedule (> 7 violations).

Starting from Visit 2, visits can be postponed by up to 14 days (inclusive) due to AEs or by up to 7 days (inclusive) due to other reasons (for all patients; if the date of a visit with BCD-085/placebo administration has to be shifted by more than 3 days, dates of the subsequent injections also should be shifted. The first postponement day is the day after the visit date). Other cases of visit re-scheduling must be agreed with the Sponsor.

A severe violation of visit time windows from Week 0 to Week 52 is a postponement of a visit by more than 7 days (due to any reasons) and by more than 14 days (due to AEs). All cases

when visits have to be postponed by more than 7 days (due to any reasons) or by more than 14 days (due to adverse events) must be agreed with the Sponsor. In case of more than 7 severe violations of visit time windows, the patient is considered non-compliant and is withdrawn from the study.

Compliance criteria for the extension and follow-up periods (Week 54 to Week 170)

- The patient who misses 20% or more injections of the investigational product during the extension study period (5 or more injections for patients initially randomized to Arms 1 and 2; 6 or more injections for patients initially randomized to Arm 3) or misses 2 or more consecutive visits/injections will be withdrawn from the study.
- Visit 22 can be postponed by up to 21 days (inclusive) due to any reasons. If the visit has to be postponed by more than 3 days, dates of subsequent visits should be shifted accordingly.
- Visits 23 and 23-1 can be postponed by 7 days (inclusive) due to reasons not related to safety and by up to 14 days (inclusive) due to safety reasons. If the date of a visit with the investigational product administration has to be shifted by more than 3 days, dates of the subsequent injections also should be shifted.
- A self-injection of the investigational product can be postponed by not more than 3 days. The patient should record the actual injection date and specify the reason for the postponement.
- Starting from Visit 24, not more than 2 consecutive visits or a total of 3 visits can be postponed by up to 14 days (inclusive) due to objective reasons (the patient cannot come to the study site due to force-majeure or any other justifiable reasons) or due to AEs. If the date of a visit with the investigational product administration has to be shifted by more than 3 days, dates of the subsequent injections also should be shifted.

All cases when visits have to be shifted by the periods exceeding those specified above must be agreed with the Sponsor.

7. ASSESSMENT OF EFFICACY

7.1 List of efficacy variables

7.1.1. Definition of variables

The patient is considered a PASI 75 responder if the PASI score improves by 75% from baseline. PASI 90 and PASI 100 responders are defined in the same way.

7.1.2. Efficacy endpoints

7.1.2.1. Primary endpoint

- Proportion of patients who achieved PASI 75 at Week 12, by study arms.

7.1.2.2. Secondary endpoints in the main treatment period (Week 0 to Week 54):

- Proportion of patients who achieved PASI 75/90/100 at Weeks 8, 16, 24, 42 and 52, by study arms.
- Proportion of patients with sPGA score 0 or 1 at Weeks 8, 12, 16, 24, 42, and 52.
- Proportion of patients with sPGA score 0 at Weeks 16, 24, 42, and 52.
- Relative change from baseline in PASI score at Weeks 8, 12, 16, 24, 42 and 52.
- Change from baseline in itch severity measured with visual analog scale (0 mm to 100 mm) at Weeks 1, 12, 24, and 52.
- Change from baseline in Nail Psoriasis Severity Index (NAPSI) score at Week 12, 24, and 52.
- Change from baseline in Dermatology Life Quality Index (DQLI) score at Weeks 8, 12, 24, 42, and 52.
- Proportion of patients with DLQI score 0 or 1 at Weeks 24, 42, and 52.
- Proportion of patients (among those with psoriatic arthritis) who achieved an ACR20/50/70 at Weeks 12, 24, and 52.

7.1.2.3. Efficacy endpoints during the extension study period (Week 54 through Week 166)

- Proportion of patients who maintained PASI 75/90/100 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Proportion of patients who maintained sPGA 0-1 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Proportion of patients who maintained sPGA score 0 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Proportion of patients who maintained DLQI score 0-1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Time to loss of PASI 75/90/100, sPGA 0-1/sPGA 0, DLQI 0-1 response during the treatment with BCD-085.
- Proportion of patients who maintained ACR 20/50/70 response (among patients with psoriatic arthritis) after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment vs. response after 52 weeks of treatment with BCD-085.
- Proportion of patients who achieved PASI 75/90/100 response after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Proportion of patients with sPGA score 0 or 1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of the treatment with BCD-085.
- Proportion of patients who achieved sPGA score 0 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Change from baseline in itch severity measured with visual analog scale (0 mm to 100 mm) after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Change from baseline in Nail Psoriasis Severity Index (NAPSI) score after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085 (among patients with nail psoriasis at baseline).

- Proportion of patients who achieved DLQI score 0 or 1 after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.
- Change from baseline in Dermatology Life Quality Index (DQLI) score after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.

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

7.2.1 Timeframes for analysis of efficacy variables

The efficacy analysis by the primary endpoint (PASI 75) will be performed after **12 weeks** of blinded therapy with BCD-085/placebo.

The timing for 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

The efficacy will be assessed in the ITT (intent-to-treat) population, which includes all randomized patients.

In addition, the efficacy can be evaluated in the PP (Per Protocol) population, which includes those patients who completed all visits without major protocol deviations.

8. ASSESSMENT OF SAFETY

8.1. List of safety variables

8.1.1. Terms and 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 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 the first dose of the investigational product and until the end of the protocol-specified follow-up period.

Negative medical events that occurred before the administration of the investigational product (including those found at Visit 1 but before the administration of the investigational product) are not considered to be adverse events. These conditions are background for this patient.

8.1.1.2. Serious adverse events

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

- Results in death;
- Is life-threatening;
- Requires hospitalization or prolongation of existing hospitalization;
- 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 a serious adverse event.

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 that resolved without any signs of hepatic insufficiency will not be considered life-threatening, although more severe hepatitis can lead to fatal outcome. Similarly,

an allergic reaction resulting in face angioedema will not be considered life-threatening despite the fact that larynx angioedema, allergic bronchospasm or anaphylaxis may lead to a 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 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 the study file.
- Hospitalization because of a previous condition (recorded before the patient signed the ICF), for example, hospitalization for kidney transplantation because a donor organ has become available, surgery for cataract diagnosed before the patient signed the ICF, etc.

Disability is defined as a significant or persistent loss of the ability to work because of a disease, injury, their consequences or other reasons during a definite period (temporary disability) or a long indefinite period.

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

- Drug administration errors, such as unintended or accidental use, whether or not associated with an AE (including confusion or possible confusion during the administration of investigational products).
- Overdose.
- Pregnancy in study subjects or their sex partners.

8.1.1.3. Unexpected adverse events

Unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (Investigator's Brochure).

8.1.2. Safety endpoints

- Proportion of patients who developed AEs/SAEs.
- Proportion of patients who developed injection site reactions.
- Proportion of patients who developed Grade 3/4 AEs/SAEs.
- Proportion of patients who discontinued the study due to AEs and/or SAEs.
- Exposure adjusted incidence rate of AEs/SAEs during the extension study.

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

8.2.1. Timeframes for analysis of safety variables

Tolerability and safety endpoints will be analyzed at Weeks 12 and 54 of the study.

Information about serious adverse events will include data on SAEs developed from the time when the subject received the first dose of the investigational product until the time he/she completed the study (as planned or prematurely).

SAEs that developed during screening will be analyzed separately. Formally, these occurrences are not considered adverse events, because they develop before the administration of the investigational product. However, they can show the safety of screening procedures or be a reason to reject the patient during the screening, so they should be recorded.

The adverse events that do not meet the seriousness criteria should be recorded starting from the moment when the investigational product was injected the first time until the end of the Protocol-defined follow-up period after the patient stopped taking the investigational product (as planned or prematurely).

Drug Safety Division of JSC BIOCAD will analyze information about every SAE immediately after receiving an SAE report, provided that the investigator sent the report(-s) within the due time window. The cumulative analysis will be performed during the preparation of the final study report.

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

8.2.2. 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 data and vital signs,
- CBC, blood chemistry, and urinalysis results,
- ECG findings.

The frequency of these procedures is specified in section 4.6.1 “Schedule of study visits and procedures”. AEs/SAEs will be documented and reported in accordance with the Sponsor’s Manual.

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

AEs are recorded beginning from the moment when the investigational product was injected the first time until the end of the follow-up period after the patient stopped taking the investigational product (as planned or prematurely). SAEs are recorded from the moment when the subject signed the informed consent form until the moment when he/she completed the study (as planned or prematurely). SAEs that were recorded during screening are not included in the total safety analysis. The Investigator can record an SAE later than stipulated by the Protocol if he/she believes that this SAE is related to the investigational product or study procedures.

An AE is considered to be resolved if the laboratory parameter, vital sign or symptom has returned to its baseline value. For all parameters, the baseline level is considered the value/sign severity that was seen in this patient before the first injection of BCD-085/placebo at the first scheduled visit per protocol. For AEs, including SAEs, of long-lasting/chronic nature, the resolution is the stabilization of the patient’s condition. For example, the AE “aggravation of chronic bronchitis” is considered to be resolved when the patient has achieved remission.

The Investigator must document non-serious AEs in the source documents and in the CRF, and show them to the Monitor at the next monitoring visit. Besides being recorded in the source documents and eCRF, serious adverse events (SAEs) must be reported to the Sponsor within 24 h in the SAE Report Form. SAE Report Forms must be sent to the Sponsor within 24 h by email to

[redacted] (email subject: "For Pharmacovigilance Officer"). The investigator should receive a receipt/delivery confirmation.

8.3 Requirements for reports, procedures for registration and reporting AEs, and filling out AE Report Forms

8.3.1. Recording AEs/SAEs

At every visit, a record should be made whether or not any AE occurred during the period from the previous visit. Any adverse event reported for a patient since he/she signed an informed consent form had to be recorded in source documents and in a special form for registration of adverse events (attachment to the CRF). AEs will be documented in accordance with the Sponsor's Manual.

AEs are recorded and numbered consecutively as they occur. Each AE is reported in an *AE Report Form*. Rules for documenting AE/SAE are described in detail in the Sponsor's Manual.

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

Laboratory and vital sign abnormalities

Laboratory and/or 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) must be recorded in the CRF, *Adverse Events* section. CTCAE 4.03 grade 1 adverse events are registered only if the investigator considers the event clinically meaningful. Starting from CTCAE 4.03 grade 2, all adverse events should be recorded, regardless of their clinical significance. It is preferable to specify diagnosis rather than individual symptoms (for example, anemia instead of reduced hemoglobin). Laboratory abnormalities meeting the criteria for an adverse event should be followed up until they return to normal or until an adequate explanation is obtained.

Special rules for AE registration

- Aggravation or worsening of the main disease or any symptoms of the main disease are not reportable as AEs **even if they have any seriousness criteria.** The event should not be documented as an SAE if hospitalization is the only seriousness

criterion, while the AE is represented by worsened signs or aggravation of the main disease.

- If the patient had no clinical/laboratory abnormalities at baseline, any grade 2 or higher (grade 1 or higher if the investigator considers it clinically meaningful) clinical/laboratory abnormality must be documented as an AE. If the patient had clinical/laboratory or other abnormalities at baseline, any increase in severity of this abnormality or any other worsening judged by the Investigator as clinically meaningful must be reported as an AE.
- The event should not be documented as an SAE if hospitalization is the only seriousness criterion, while the AE is represented by worsened signs or aggravation of the main disease.
- Cases of confirmed[125] positive results of Diaskintest, QuantiFERON or T-spot are recorded as adverse events.

Injection site reactions

In this clinical study, investigators will evaluate injection site reactions after the administration of BCD-085/placebo. Assessments will be performed on the same visits when injections will be given. Assessment includes visual examination of the injection site (and sites where injections were given in the past if this is not the first visit) and collection of patient's complaints. The Injection Site Reaction Form is presented in Annex 1. The Injection Site Reaction Report Form should be filled out only if an injection site reaction is recorded (starting from grade 1). If there are no injection site reactions, this form is not filled out. Injection site reactions of grade 2 or higher must be registered as adverse reactions. If the investigator considers a grade 1 injection site reaction to be clinically meaningful, it also must be registered as an adverse event. Severity grades for injection site reactions are presented in Annex 1.

Among other laboratory/vital sign/clinical abnormalities not found at Visit 1 before the first injection of the investigational product, the following is recorded:

- All abnormalities of CTCAE 4.03 grade 2 and higher.
- Grade 1 abnormalities should be recorded as AEs only if clinically relevant, i.e. if the Investigator considers the abnormality to be substantial with account of the main and concurrent illnesses. Single abnormalities found among multiple laboratory test results or

[125] If retest is performed, its results are considered.

incidental low values should not be reported as AEs, except for events that are clinically relevant.

If revealed during the period between scheduled visits (for example, when the patient comes to the study site for dialysis), a laboratory/vital sign/instrumental abnormality can be recorded by the Investigator in the eCRF if clinically meaningful (regardless of its severity grade). The Investigator specifies the onset date, the fact that the AE occurred between visits, and the reason why the AE was recorded (for example, numerical values of laboratory and/or vital signs).

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 no data are available, “Data not available” or “N/A” are put. 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:

- Sec. No. of AE,
- Visit number,
- A brief description of the AE,
- Serious (yes/no),
- Seriousness criteria (if applicable),
- Severity grade and highest severity grade according to CTCAE 4.03,
- Onset date,
- End date,
- Outcome,
- Actions taken,
- Causality,
- Comments specifying any clinically relevant (in the Investigator’s opinion) information related to AE development or therapy.

If a medication therapy was administered, its components are 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* are filled using digital codes explained in the *Notes* section. If the investigator considers an AE to be an SAE, he/she fills out an SAE Report Form in addition to the AE Report Form (printed copies).

One SAE Report Form is filled out for one SAE. If the AE remains unresolved at the next visit, the checkbox in the *Adverse Events* section of the eCRF should be ticked for this visit and marked as "unresolved". If any new important information has become available, a follow-up SAE Report Form should be filled out and sent to the Sponsor. If no new information about the SAE is available, the recommended frequency of reporting is once every 14 days.

The following information should be recorded in the SAE Report Form:

1) Clinical study:
   - Protocol ID,

2) SAE information:
   - SAE name,
   - Initial or follow-up,
   - Internal SAE code assigned by the Sponsor (this field is filled out by the Sponsor)

3) SAE reporting investigator and study site:
   - Full name of the investigator who reported the SAE
   - Contact information (tel. and e-mail)
   - Site name and code
   - Full name of the Principal Investigator

4) Information on the study subject:
   - Subject's number
   - Sex
   - Body weight
   - Height
   - Date of birth
   - Renal/hepatic impairment
   - Allergies

5) Information on the test drug:
   - Code (or trade name) of investigational product
   - Indication
   - Date of the first dose

- Batch of the investigational product (after which the event developed)
- Dose (with which the event occurred)
- Treatment start date and time (followed by the event)
- Treatment stop date and time (followed by the event)
- Route of administration
- Doses and dosing frequency

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

- INNs and brand names of concomitant medications
- Indication
- Start date
- End date
- Doses, 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 time frames indicated.
- Time after the last dose of the investigational product
- Autopsy data if the subject died (specify the cause of death according to postmortem report). 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 the onset of the SAE

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

12) Actions taken to resolve the SAE

- Medications/other

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 reduced/unchanged etc.
- 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.

8.3.3. Reporting cases of study subject's pregnancy/study subject's partner's pregnancy

In this study, the Investigator must report to the Sponsor all cases of study subject's pregnancy/study subject's partner's pregnancy that occurred during the study treatment period and follow-up after the last injection of BCD-085/placebo.

The forms are filled out in the following cases:

- When the initial information about the study subject's pregnancy/study subject's partner's pregnancy is obtained;
- When new important information (follow-up report) about the pregnancy (its complications or outcome) is obtained;
- In 6 months after the delivery, so that the baby's condition can be assessed.

The report about pregnancy NOT associated with an SAE should be sent to the Sponsor by e-mail to [redacted] within 5 working days.

If an SAE has developed during pregnancy, the Pregnancy Form with the information about the SAE must be sent to the Sponsor within 24 h after this information became available.

8.3.4. Recording administration errors with the investigational product

Administration errors with the investigational product refer to any violation of dosing, route or procedure of administration described in the Study Protocol. This also includes violation (prolongation) of the interval between the doses of the investigational product, except for the cases specified by the protocol.

This form is filled out for all these errors except for overdoses.

If an administration error with the investigational product is associated with an SAE, an SAE Report Form should be also filled out.

If an investigational product administration error is not associated with an SAE, the Investigator should send the form by email to safety@biocad.ru within 5 working days.

If an administration error with the investigational product is associated with an SAE, two forms are filled out (SAE Report Form and IP Administration Error Report Form). Both forms must be sent to the Sponsor within 24 hours from the moment when this information became available.

8.3.5. Reporting drug overdose

In this study, an overdose is defined the following way: administration of BCD-085 at a single dose greater than 120 mg or shortening of the interval between two doses by more than 3 days. Shortening the between-visit periods by 3 days or less is not considered an overdose.

Criteria for expedited reporting in case of overdoses:

- An overdose of 2-fold or more vs. the dose prescribed by the Investigator must be reported as part of expedited reporting whether it is associated with an AE/SAE or not;
- An overdose of less than 2-fold associated with an AE/SAE with a reasonable temporal relationship to the overdose also requires expedited reporting;
- An overdose of less than 2-fold not associated with AEs/SAEs may be reported to the Sponsor as part of expedited reporting if, in the opinion of the Investigator, this event is meaningful;

If the Investigator did not report an overdose of less than 2-fold using expedited reporting, the overdose should be recorded by the CRA only in the Deviations Log.

8.4. Methods and duration of follow-up for study subjects after the onset of AE/SAE

If the patient is withdrawn from the study due to an AE/SAE, the investigator should perform further patient's treatment and follow-up as per standard institutional practices for the treatment of the certain AE or 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, if possible, be followed up until the event 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 throughout 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 woman'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. The pregnancy course, its outcome, and the newborn are followed up only if the patient gives her consent in the written form. The consent should be signed by the patient and stored in the source documentation. Any time, the patient could refuse from the follow-up/providing information about her pregnancy/its outcome/the newborn.

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 the woman's health over the entire course of pregnancy. Monitoring should be performed via phone calls to attending Ob/Gyn Specialist once every 3 months to analyze the overall woman's health, pregnancy course, and laboratory and instrumental findings including ultrasonic investigation. 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. The pregnancy course, its outcome, and the newborn are followed up only if the woman gives her consent in the written form. The consent should be signed by the woman and stored in the source documentation. Any time, the woman may refuse from the follow-up/providing information about her pregnancy/its outcome/the newborn.

8.5. Immunogenicity study

To assess the immunogenic potential of the study treatment, the proportions of BAb- and NAb-positive patients will be estimated.

The immunogenicity endpoints will be evaluated at Weeks 12, 24, 54, 86, 110, 134, 154 (in patients of Arms 1 and 2) or 12, 24, 54, 64, 98, 122, 146, 166 (in patients of Arm 3).

The immunogenicity analysis will include all patients who have received at least one dose of BCD-085 and had an evaluable (not missing/lost/spoiled) serum sample taken before the first

dose of BCD-085 and at least one evaluable (not missing/lost/spoiled) serum sample taken at subsequent visits.

9. STATISTICS

9.1. Description of statistical methods

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

To compare normally distributed data, it is planned to use the following tests: two-sample Student t-test, Welch's test, and ANOVA.

Non-normally distributed data will be compared with the following tests: Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test, and Friedman test.

The quantitative data:

Efficacy:

- Relative PASI change,
- Change in itch severity (VAS, 0 to 100 mm),
- Change in NAPSI score,
- Change in quality of life according to the DLQI score,
- Time to loss of PASI 75/90/100, sPGA 0-1/sPGA 0, DLQI 0-1 response during the treatment with BCD-085.

Safety:

- CBC results,
- Blood chemistry results.

Demographics

will be tested for the normality of distribution using the Shapiro-Wilk test.

For normally distributed quantitative data, the following characteristics will be used: mean value, standard deviation, coefficient of variation, minimum and maximum. Non-normally distributed quantitative data will be described using median and quartiles, min and max values.

The categorical data:

Efficacy:

- Proportion of patients with PASI 75/90/100.
- Proportion of patients with sPGA score 0 or 1.
- Proportion of patients (among patients with psoriatic arthritis) who achieved an ACR20/50/70.
- Proportion of patients who maintained ACR 20/50/70 response (among patients with psoriatic arthritis).
- Proportion of patients who maintained DLQI score 0-1.

Safety:

- Proportion of patients who developed AEs/SAEs.
- Proportion of patients who developed injection site reactions.
- Proportion of patients who developed Grade 3/4 AEs/SAEs.
- Proportion of patients who discontinued the study due to AEs and/or SAEs.
- Exposure adjusted incidence rate of AEs/SAEs during the extension study.

Immunogenicity:

- Proportion of patients with anti-drug antibodies (binding/neutralizing)

will be processed using the frequency tables, Fisher's test, χ^2 test, and Cochran-Mantel-Haenszel test. The categorical data will be described using percentages or proportions.

For multiple comparisons, the Benjamini-Yekutieli procedure will be used. Regression will be used to assess the effects of the factors other than the therapy type. Time to loss of response will be assessed using log-rank test, Kaplan-Meier curves, and Cox regression model. Time will be counted from the response during the treatment with BCD-085. Right censoring can be used to analyze time to events.

Statistical methods will be chosen based on the type and distribution of raw data. Applicability of certain statistical tests will be evaluated after all the data are collected because it is impossible to predict the distribution pattern, data homogeneity and other data characteristics in advance.

The data will be processed using programming language R for statistical processing and SAS 9.4 software environment.

9.2. Statistical analysis steps and timelines for reports

[redacted]

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

Two independent hypotheses will be tested during the study:

1. The main study hypothesis (stating the non-inferiority of BCD-085 Q4W vs. BCD-085 Q2W) will be tested at the significance level of 0.05;
2. The hypothesis stating the superiority of BCD-085 in different dosing regimens over placebo will be tested at the significance level of 0.05.

9.3.1. Non-inferiority hypothesis

The sample size required to run the study was calculated on the basis of the literature data on clinical efficacy. During study planning, the hypothesis stating that BCD-085 Q4W is non-inferior to BCD-085 Q2W ($H_0: \varepsilon \leq \delta$, $H_1: \varepsilon > \delta$, where ε is true difference in the frequency of the efficacy variable between the arms, δ is non-inferiority margin) was tested with the following error values: type I error of 5% (α=0.05), type II error of 20% (β=0.2), power of test of 80%. The

efficacy endpoint used to calculate the sample size was PASI 75 rate by Week 12 in each arm [redacted]

[redacted]

1. Efficacy variable in the arms: BCD-085 every 2 weeks (p_{2w}) and BCD-085 every 4 weeks (p_{4w}):

   p_{2w} = 0.891 (89.1%)

   p_{4w} = 0.826 (82.6%)

2. The true difference in the rates of the efficacy parameter between two regimens of BCD-085:

   $\varepsilon = p_{4w} - p_{2w}$ =0.826 – 0.891= (-0.065) (6.5%)

3. $z_{1-\alpha}$ and $z_{1-\beta}$ – quantiles of normal distribution N(0,1) (mean: 0, standard deviation: 1).

4. k – coefficient for ratio between sample sizes [BCD-085 Q2W (n_{2w}) to BCD-085 Q4W (n_{4w})]:

   $n_{2w}/n_{4w} = k$.

5. The non-inferiority margin for BCD-085 once every 4 weeks vs. BCD-085 once 2 weeks was considered to be the following:

   δ= (-0.2038) (-20.38%)

[redacted]

After that, in accordance with the method described in [Chow Sh.-Ch., Shao J., Wang H., 2008], sample size was calculated using the assumption that sample sizes of the BCD Q4W (n_{4w}) arm and the BCD Q2W (n_{2w}) arm are the same, i.e. k = 1.

[redacted]

[redacted]

9.3.2. Superiority hypothesis

Sample size for superiority testing

During study planning, the hypotheses stating that BCD-085 Q4W and BCD-085 Q2W are superior to placebo (H_{01}:$\varepsilon_{2w} \leq \delta$, H_{11}:$\varepsilon_{2w} > \delta$; H_{02}:$\varepsilon_{4w} \leq \delta$, H_{12}:$\varepsilon_{4w} > \delta$, where ε_{2w}, ε_{4w} is the true difference in the rate of the efficacy variable between the arms treated with BCD-085 Q2W and with BCD-085 Q4W, respectively, δ is the superiority margin for BCD-085 over placebo) were tested with the following error values: type I error of 5% (α=0.05), type II error of 20% (β=0.2), power of test of 80%. The efficacy endpoint used to calculate the sample size was PASI 75 rate by Week 12 in each arm [redacted]

The sample size needed to test the superiority hypotheses was calculated using the method described by [Chow Sh.-Ch., Shao J., Wang H., 2008]:

1. Efficacy variable in the arms: BCD-085 every 2 weeks (p_{2w}), BCD-085 every 4 weeks (p_{4w}) and placebo (p_{Pl}):
   p_{2w} = 0.891 (89.1%)
   p_{4w} = 0.826 (82.6%)
   p_{Pl} = 0.039 (3.9%)

2. The true difference in the frequency of the efficacy variable between the test/comparator and placebo arms:

   $\varepsilon_{2w} = p_{2w} - p_{pl} = 0.891 - 0.039 = 0.852$
   $\varepsilon_{4w} = p_{4w} - p_{pl} = 0.826 - 0.039 = 0.787$

3. $z_{(1-\alpha)}$ and $z_{(1-\beta)}$ – quantiles of normal distribution N(0,1) (mean: 0, standard deviation: 1).
4. k – ratio between the test and control samples:

[redacted]

$n_{pl}/n_{2w} = 1$

$n_{pl}/n_{4w} = 1$

5. The superiority margin for BCD-085 (different regimens) over placebo was set as 0, as required to check the non-inferiority hypothesis in a placebo-controlled study[128]:

$\delta = 0$.

[redacted]

Thus, the study should include at least 193 patients (77 in each BCD-085 arm and 39 in placebo arm). With a potential dropout rate of 10%, the study should involve 213 patients (85 patients in each BCD-085 arm and 43 patients in the placebo arm).

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 stopping and/or terminating the study

Not specified by the Protocol.

[128] "Non-Inferiority Clinical Trials to Establish Effectiveness", FDA, 2016.

9.6. Handling of missing, unevaluable or uncertain data

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

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 Data Manager and Medical Expert generate queries, which are patient- and site-specific, i.e. generated for each subject individually. The CRA sends queries to the study site 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 the queries are received from investigators, the employee keeping the database checks them for inconsistencies, errors, and missing data points When all the data from all the sites are collected and entered, the database is locked, and the statistical processing can be performed.

Missing, unevaluable or uncertain data are not subject to replacement.

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 randomized in the study.

Efficacy analysis

The efficacy will be assessed in the ITT (intent-to-treat) population, which includes all randomized patients.

In addition, the efficacy can be evaluated in the PP (Per Protocol) population, which includes those patients who completed all visits without major protocol deviations.

Immunogenicity analysis

The immunogenicity analysis will include all patients who have received at least one dose of BCD-085 and had an evaluable (not missing/lost/spoiled) serum sample taken before the first dose of BCD-085 and at least one evaluable (not missing/lost/spoiled) serum sample taken at subsequent visits.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution involved in the study must ensure direct access to source data/documents during monitoring, audits, ethics review, and inspections by regulatory authorities.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data quality assurance

According to the ICH GCP and regulatory requirements, the Sponsor, a 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 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. Investigator's adherence to the Protocol

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 prior written permission from JSC BIOCAD, the Ministry of Healthcare of the Russian Federation, and the Local Ethics Committee, except when necessary to protect patients from an immediate hazard.

The investigator should have enough time to accurately perform and complete the study within the timeframes 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 the 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 subject 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 CJSC 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

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

The investigators must ensure that data are entered in the eCRFs in a timely manner, and must give the Sponsor's representative (CRA) regular access to the eCRFs, patient medical records, and all other study materials. 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 completion of the study, the BIOCAD's representative (Clinical Study Manager or CRA) will visit the study site for a closeout 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 studies 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 due to other reasons. If JSC BIOCAD suspends or terminates the study, the study site will be notified in advance. If JSC BIOCAD suspends or terminates the study, CJSC BIOCAD and the investigator must promptly inform the IRB/IEC and regulatory authorities. 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 set forth in the Helsinki Declaration of the World Medical Association, Russian Federal Law "On circulation of medicinal products" (FZ-61 dated April 12, 2010), Russian Decree N 200n dated April 01, 2016 "On approval of Good Clinical Practice", Russian National Standard "Good Clinical Practice" (GOST R 52379-2005), Good Clinical Practice of the Eurasian Economic Union, Constitution of the Russian Federation, Federal Law 323-FZ dated November 21, 2011 "On fundamental healthcare principles in the Russian Federation", GCP and regulatory requirements of the participating countries.

Before the study start, the final version of the Protocol, including Patient Information Sheet and Informed Consent Form, will be submitted for approval to Russian regulatory authorities 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 necessary. Local Ethics Committees will also be notified of all SAEs that are related, in the 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 subject gets 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 study subjects, the text of this Protocol, and all other study materials and results.

The Investigator must ensure subject 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 subjects' IDs, last names, addresses, phone numbers, and medical record numbers (if applicable). The investigator must keep the confidentiality of the data not intended for submission to JSC BIOCAD.

All study materials proprietary to JSC BIOCAD cannot 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 are the essential documents that 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 approval from JSC BIOCAD before destroying any of the essential documents. Appropriate measures must be taken to prevent 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 informing study subjects and obtaining their written authorization regarding 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, if 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. If the patient recalls authorization to collect or use his/her protected health information, the investigator should do as much as possible to get patient's permission for collecting at least the safety information (i.e. onset of new or aggravation of existing adverse events) until the scheduled end of the study period.

To prevent unauthorized access to protected subject information, the data management system uses integrated safety elements encrypting all the data when sending them in both directions. The access to the system will be controlled via individually assigned ID codes and user passwords issued only to authorized and adequately trained personnel.

[redacted]

[redacted]

13.3. Collection of data

This study 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 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 the 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.

14. REIMBURSEMENT AND INSURANCE

Patients will not be paid for participation in this study. 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 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.

The insurance covers claims of study subjects to the Insurer only for compensation for harm for their life and health during the participation in the clinical study. The insurance interest is the patient's property interest related to harm for his/her life or health due to the clinical study in case of the causal relationship between the participation in the study and the insured event.

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

a) In case of death of the insured person - [redacted]. The insurance benefit is divided into equal parts and paid to beneficiary parties;

b) If the insured person gets injured, and the injury results in:

Group I disability: [redacted];

Group II disability [redacted];

Group III disability: [redacted].

c) If the insured person gets injured, and the injury does not result in disability: not more than [redacted].

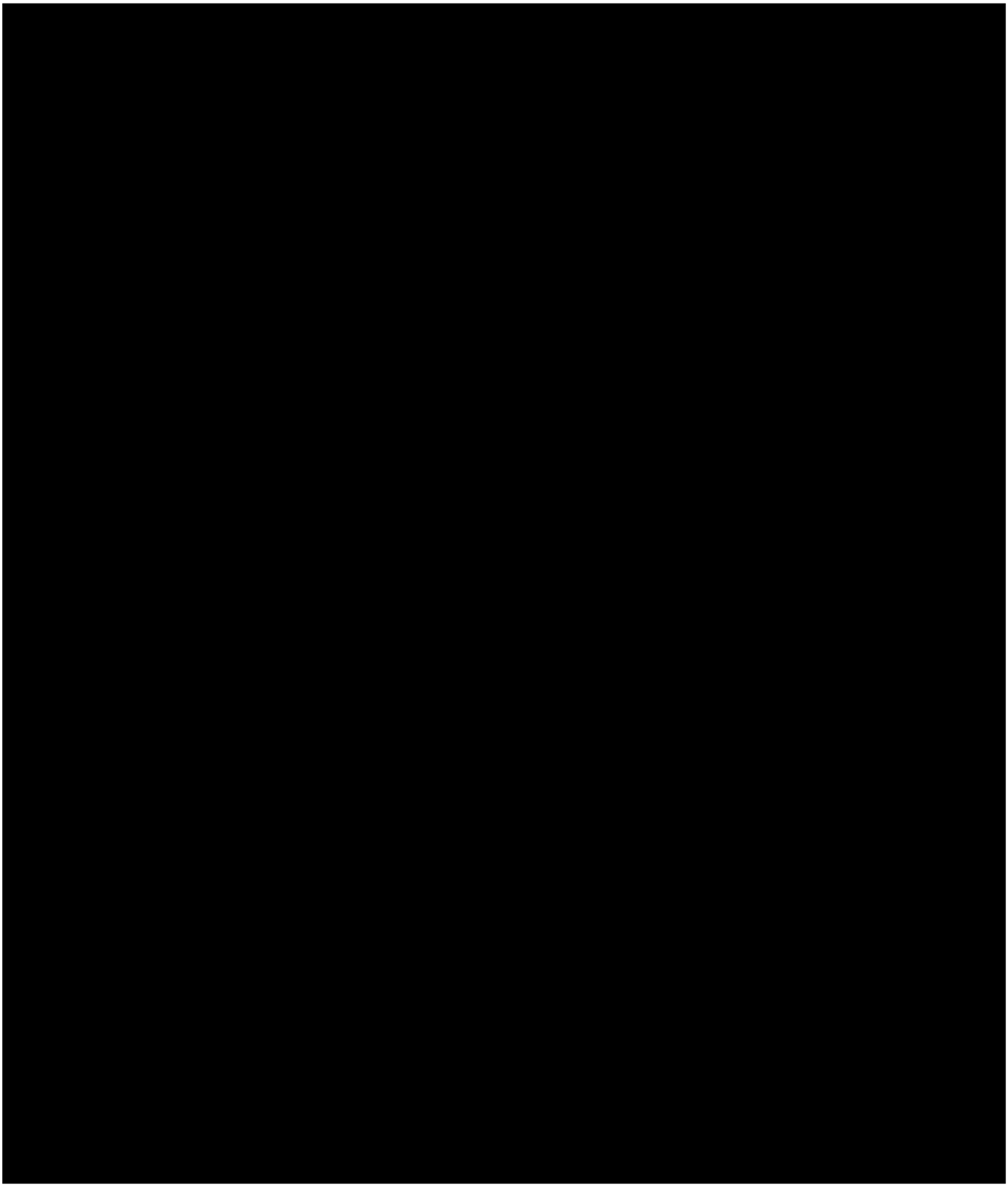
Patients in other participating countries will be insured throughout the entire study according to the law of the participating country.

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 at his/her study site, without a permit from JSC BIOCAD. Results from individual study sites must not be published before the publication of the overall study results.

16. ANNEXES

Annex 1. Injection Site Reaction Form



Annex 2. VAS for assessing itch severity (template)

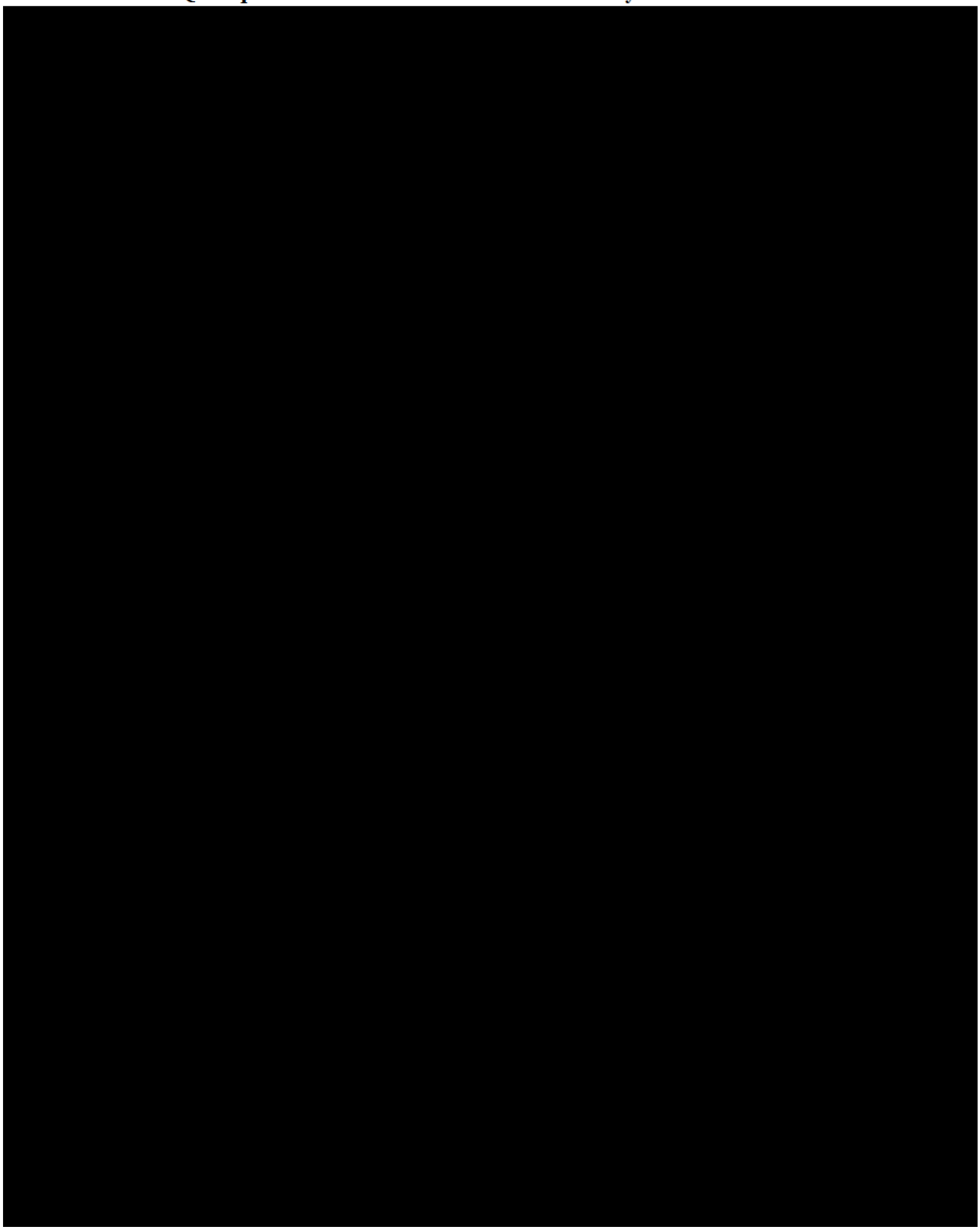
Annex 3. VAS for assessing psoriatic arthritis (templates)

1. Psoriatic arthritis activity assessed by the physician

2. Patient assessment of pain

3. Psoriatic arthritis activity assessed by the patient

Annex 4. HAQ-DI questionnaire to assess functional activity



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