STATISTICAL ANALYSIS PLAN

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**
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology criteria of improvement in rheumatoid arthritis
AE	Adverse event
ANOVA	Analysis of variances
BCD-085	A monoclonal anti-IL17 antibody manufactured by JSC BIOCAD
BMI	Body mass index
BSA	Body surface area affected by psoriasis
CBC	Complete blood count
CI	Confidence interval
CV	Coefficient of variation
DLQI	Dermatology Quality of Life Index
HAQ-DI	Health assessment questionnaire disability index
ICF	Informed consent form
IL	Interleukin
ITT	Intent-to-treat
JSC	Joint Stock Company
MAb	Monoclonal antibody
NAb	Neutralizing antibodies
NAPSI	Nail Psoriasis Severity Index
PASI	Psoriasis Area and Severity Index
PP	Per protocol
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
sPGA	Static Physicians Global Assessment
TNF-α	Tumor necrosis factor alpha
UV	Ultraviolet
VAS	Visual analogue scale

1. INTRODUCTION

The Statistical Analysis Plan (SAP) provides a detailed analysis plan and steps of study report preparation for the clinical trial BCD-085-7.

2. GOALS AND OBJECTIVES

2.1. Purpose

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.

2.2. Objectives

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).

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).

2.3. Hypothesis

Two independent hypotheses will be tested during the study:

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

3. STUDY DESIGN

3.1 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, 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).

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, inclusive).
3. Extension treatment 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.

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 subcutaneous 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 subcutaneous 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.

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) subcutaneous 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:

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).

3.2 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.

4. EVALUATION CRITERIA

4.1 Efficacy endpoints

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 (VAS) (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 (DLQI) 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.

Secondary 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 (VAS) (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 (DLQI) score after 62, 74, 86, 98, 110, 122, 134, 146, and 154 weeks of treatment with BCD-085.

4.2. 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.

4.3. Immunogenicity endpoints

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

5. THE PLANNED ANALYSIS

Final report

The final report will contain results of the efficacy and safety endpoint analysis by study arms after the 12-week blinded treatment period (Week 0 to Week 12) in 213 study subjects.

Supplementary reports

Supplementary Report 1 will contain results of the efficacy and safety endpoint analysis by study arms after 54 weeks of the study.

Supplementary Report 2 will contain results of the efficacy and safety endpoint analysis after 2 years of the study treatment (110 weeks in patients from Arms 1 and 2, 122 weeks in patients from Arm 3).

Supplementary Report 3 will contain results of the efficacy and safety endpoint analysis after 3 years of the study treatment (158 weeks in patients from Arms 1 and 2, 170 weeks in patients from Arm 3).

6. SAMPLE SIZE CALCULATION

Two independent hypotheses will be tested one after another:

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.

6.1. 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 noninferior 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]

The superiority margin was calculated using the 95% confidence interval for the difference in rates between the BCD-085 Q2W and placebo arms. [redacted]

According to [Design and Analysis of Non-Inferiority Trials, M.D. Rothman, Wiens, 2012], the superiority margin can be set as half of the lower bound of the 95% CI for the difference in efficacy parameter values of the active drug and placebo. [redacted]

[redacted]

6.2. Superiority hypothesis

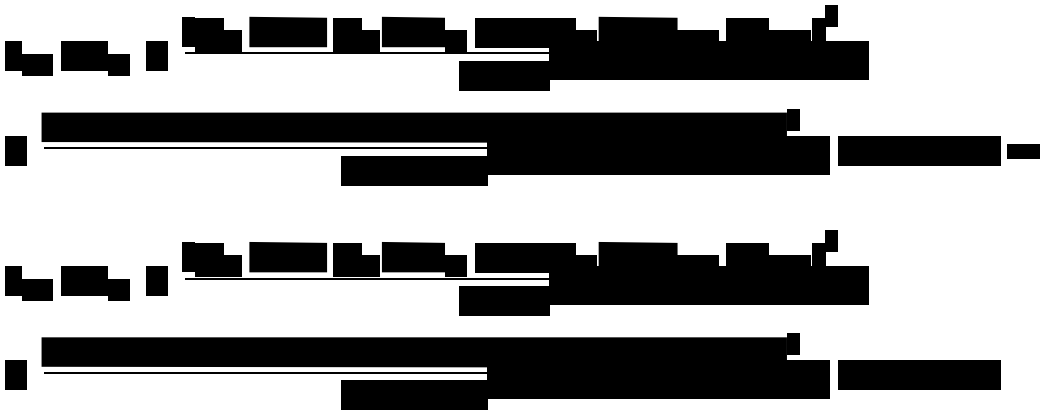
Sample size for superiority testing

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]:

[redacted]

[redacted]



[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).

7. ANALYSIS POPULATIONS

Safety analysis

The safety analysis will include all patients randomized in the study (intent-to-treat (ITT) population).

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.

[redacted]

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.

Main demographics, baseline clinical and laboratory parameters obtained on the screening will be processed using descriptive statistics and will be analyzed in the efficacy and safety populations.

8. ANALYSIS PLAN AND STATISTICAL METHODS

8.1. The software

Statistical processing of the data will be performed using R programming language for statistical computing and SAS 9.4 environment.

8.2. Description of the Statistical Methods to be Employed

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

The study hypothesis of non-inferior efficacy of BCD-085 once every 4 weeks vs. BCD-085 once every 2 weeks will be proved by comparing the lower bound of the 95% confidence interval for the difference in proportions of patients with PASI 75 at Week 12 between the BCD-085 Q4W and BCD-085 Q2W with pre-specified non-inferiority margin (δ) equal to -20.38%.

The hypothesis stating the superior efficacy of BCD-085 over placebo will be proved by comparing the lower bound of the 95% confidence interval for the difference in proportions of patients with PASI 75 by Week 12, in each BCD-085 arm and placebo arm, with pre-specified non-inferiority margin (δ, 0%).

Quantitative Data

The following quantitative data will be analyzed in the study:

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,
- Vital signs,

Demographics and other baseline characteristics:

- General information (age, body weight, height, BMI),
- Duration of the disease, severity and the area of psoriasis (PASI), BSA, severity by sPGA, severity of nail psoriasis (NAPSI), severity of pruritus (VAS), quality of life score (DLQI), the presence of depression (Beck's score), functional activity (HAQ-DI), tender joint count (of 68) , swollen joint count (of 66).

Quantitative data will be described using the following descriptive statistics: mean, SD, median, quartiles, CV, min, and max.

Quantitative variables will be tested for normality using the Shapiro-Wilk test.

Normally distributed quantitative variables will be tested using the two-sample Student's t-test, Welch's t-test, and ANOVA.

Non-normally distributed quantitative variables will be tested using the Mann-Whitney U-test, the Wilcoxon test, the Kruskal-Wallis test, and the Friedman test.

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.

Categorical Data

The following categorical data will be analyzed in the study:

Efficacy:

- Proportion of patients with PASI 75/90/100,
- Proportion of patients with sPGA score 0 or 1,
- Proportion of patients with DLQI score 0 or 1,
- Proportion of patients (among patients with psoriatic arthritis) who achieved an ACR20/50/70,
- Proportion of patients who maintained PASI 75/90/100 score,
- Proportion of patients who maintained sPGA score 0 or 1,

- Proportion of patients who maintained DLQI score 0 or 1,
- Proportion of patients who maintained ACR 20/50/70 response (among patients with psoriatic arthritis).

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).

Demographics and other baseline characteristics:

- General information (Race, Sex, Childbearing potential (women)),
- Prior therapies for plaque psoriasis,
- Co-morbidities and the most relevant prior diseases,
- Medical history.

Extent of exposure:

- The number of administrations given during the study,
- Exposure of BCD-085 with mean daily dose and treatment duration.

Percentages or proportions will be used to describe categorical data.

Categorical data will be processed using frequency tables, the Fisher's exact test, Yates-corrected Pearson's χ^2 test, and the Cochran-Mantel-Haenszel test.

The Benjamini-Yekutieli correction for multiple testing will be used.

8.3. The level of significance to be used

The level of significance is set as 0,05 (5%) with statistical power of 0,8 (80%).

8.4. Accounting for missing, unavailable or doubtful data, outliers

Missing, unused, and spurious data will not be substituted.

Spurious and unevaluable data are revealed during the outlier analysis by examination of Mahalanobis or Cook distance, visual analysis of scatter plots and box plots.

All actions taken to handle missing, unevaluable, spurious data and outliers before/during the statistical analysis will be described in the Clinical Study Report.

8.5. Statistical evaluations for the early study termination

Not available.

8.6. Subgroup analysis, interaction and related variables

Not available.

9. OTHER PLANNED ANALYSES

No additional analyses are planned in this study.

10. DEVIATIONS FROM ANALYSIS METHODS DESCRIBED IN STUDY PROTOCOL

This Statistical Analysis Plan has no deviations from methods described in Study Protocol.