STATISTICAL ANALYSIS PLAN

Protocol Title:	**An International Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-finding Clinical Study of Efficacy and Safety of Subcutaneous BCD-085 in Patients with Moderate to Severe Plaque Psoriasis**
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ANOVA	Analysis of variances
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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
[redacted]	[redacted]
[redacted]	[redacted]
CV	Coefficient of variation
DLQI	Dermatology Quality of Life Index
IL	Interleukin
JSC	Joint Stock Company
[redacted]	[redacted]
MAb	Monoclonal antibody
[redacted]	[redacted]
[redacted]	[redacted]
NAPSI	Nail Psoriasis Severity Index
PASI	Psoriasis Area and Severity Index
[redacted]	[redacted]
QoL	Quality of Life
SAE	Serious adverse event
SF-36	Short Form Health Survey
SAP	Statistical Analysis Plan
SD	Standard deviation
sPGA	Static Physicians Global Assessment
[redacted]	[redacted]
[redacted]	[redacted]
VAS	Visual analogue scale
[redacted]	[redacted]

1. INTRODUCTION

The Statistical Analysis Plan (SAP) provides a detailed analysis plan for the clinical trial BCD-085-2.

2. GOALS AND OBJECTIVES

2.1. Purpose

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

2.2. Objectives

1. To determine the number of patients in each study arm who achieved a PASI75 at Week 12 of treatment.
2. To determine the number of patients in each study arm who achieved a PASI75 at weeks 4 and 8 of treatment.
3. To determine the number of patients in each study arm who achieve a PASI50/90 at weeks 4, 8, and 12 of treatment.
4. To evaluate the PASI score improvement from baseline at weeks 4, 8, and 12 in each study arm.
5. To evaluate the improvement in the body surface area (BSA) affected by psoriasis from baseline to weeks 4, 8, and 12 in each study arm.
6. To evaluate the improvement in the nail psoriasis severity index (NAPSI) from baseline to week 12 in each study arm.
7. To determine the mean change in the intensity of pruritus measured by VAS (0-100 mm) from baseline to weeks[1] 1, 4, 8, and 12 in each study arm.
8. To evaluate the proportion of patients in each study arm who achieved an sPGA score 0 or 1 at weeks 4, 8, and 12 relative to baseline.
9. To investigate patients' quality of life in each study arm at weeks 4, 8, and 12 according to SF-36 and DLQI.
10. To evaluate the proportion of patients in each study arm who develop adverse events with multiple injections of 40 mg, 80 mg, and 120 mg BCD-085 as compared to placebo.

[1] The Protocol (*Study goals* section) had a technical misprint and mistakenly listed Week 2 as an assessment time point for pruritus. No assessment was performed at Week 2.

[redacted]

2.3. Hypothesis

The primary hypothesis for this study is that BCD-085 is superior to placebo in patients with moderate to severe plaque-type psoriasis, as assessed by the proportion of patients who achieved a PASI 75 at Week 12.

3. STUDY DESIGN

3.1 Design

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

The study involves 120 adults with moderate to severe plaque psoriasis.

Before inclusion in the active phase of the study, patients undergo a screening exam (max duration was 28 days) to determine whether they meet the inclusion/exclusion criteria. When all screening procedures are completed and the investigator approved patient's inclusion in the study, each patient is stratified by body weight (≤80 kg / ≥81 kg), prior use of monoclonal antibodies for psoriasis (MAb-treated/MAb-naïve), current use of systemic non-biologics (yes/no), PASI score (< 20 / ≥ 20), and signs of psoriatic arthritis (yes/no). After stratification, the patients are randomized 1:1:1:1 to one of four study arms:

- **Arm 1**: Patients receive subcutaneous injections of 40 mg BCD-085 (1.0 mL) once a week for the first 3 weeks (induction period) and then once every 2 weeks (maintenance period). For blinding purposes, these patients receive two subcutaneous injections of placebo (1.0 mL each) together with each injection of BCD-085. Thus, the drug is administered on Day

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

[redacted]

1 at Week 0, Day 1 at Week 1, Day 1 at Week 2 (induction period), Day 1 at Week 4, Day 1 at Week 6, Day 1 at Week 8, and Day 1 at Week 10 (maintenance period).

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

Thus, in the active period of the study, patients are given the test drug/placebo injections weekly for the first three weeks of treatment and then once every 2 weeks. After assessment of the results at Week 12, all patients are transferred to a 4-week follow-up. During 14 weeks after the screening, 9 visits are performed to assess the efficacy, safety,

[redacted]

4. EVALUATION CRITERIA

4.1 Efficacy endpoints

Primary endpoint

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

Secondary endpoints

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

4.2. Safety endpoints

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

[redacted]

5. THE PLANNED ANALYSIS

The study report will be made after the study completion (after all included patients will finish the study). The report will present the efficacy analysis for 12 weeks of treatment and the safety [redacted] analyses over 14 weeks of the study.

6. SAMPLE SIZE CALCULATION

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

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

The efficacy criterion used to calculate the sample size was the proportion of patients with moderate to severe plaque psoriasis who achieved a PASI75 at Week 12 of ixekizumab therapy in a clinical study that had the same design as the planned study[3]. The proportion of PASI75 responders was 76.7% in the arm treated with the lowest dose of secukinumab and 7.7% in the placebo arm.

1. The efficacy in the test arm (p_T) and in the placebo arm (p_{pl}):
   p_T = [redacted]
   p_{pl} = [redacted]

2. The true difference in the frequencies between the test and the placebo arms:
   $\varepsilon = p_T - p_{pl}$ = [redacted]

3. z_α and z_β – quantiles of normal distribution N(0.1) (mean: 0, standard deviation: 1).

4. k- the ratio between the sample sizes between the arms (placebo-to-test) :
   $n_{pl}/n_T = k$.

5. The superiority margin was set as follows:
   δ= [redacted]

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

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

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

[redacted]

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

Taking all above said into account, the final sample size was set as 120 patients. This sample size allows evaluating adverse events that occur in more than 1 of 10 patients, ensures [redacted] and allows comparing the effects seen with different doses of BCD-085.

7. ANALYSIS POPULATIONS

Safety analysis

The safety analysis will include all patients who received at least one dose of BCD-085.

Efficacy analysis

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

[redacted]

[redacted]

8. ANALYSIS PLAN AND STATISTICAL METHODS

8.1. The software

Statistical processing of the data will be performed using the Statistica 10.0 package and R programming language.

8.2. Description of the Statistical Methods to be Employed

The statistical analysis will include two-tailed hypothesis testing; the chosen significance level is 0.05.

To prove the protocol-stated hypothesis of BCD-085 being superior to placebo, the 95% CIs will be calculated for the difference in proportions of PASI 75 achievement at Week 12 (individual comparisons will be performed for placebo versus each BCD-085 arm). The hypothesis will be accepted if the lower bound of the estimated 95% CI for the difference in proportions of PASI 75 at Week 12 achievement is above the pre-specified margin of clinically non-meaningful differences (δ) of [redacted]

Quantitative Data

The following quantitative data will be analyzed in the study:

Efficacy:

- The percent improvement from baseline in the PASI score in each study arm at weeks 4, 8, and 12,
- The relative improvement from baseline in the BSA in each study arm at weeks 4, 8, and 12,
- The relative improvement from baseline in the NAPSI in each study arm at week 12,
- The mean change from baseline in the intensity of pruritus measured by VAS (0-100 mm) in each study arm at weeks 1, 4, 8, and 12,
- The mean change from baseline in the QoL score in each study arm (assessed using DLQI and SF-36 scales) at weeks 4, 8, and 12,

[redacted]

[redacted]

Safety:

- CBC results,
- Blood chemistry results,
- Coagulation pattern,
- 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), and the quality of life score (SF-26 and DLQI).

Quantitative data will be described using the following descriptive statistics: mean, SD, geometric mean (for the pharmacokinetic data), 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.

Categorical Data

The following categorical data will be analyzed in the study:

Efficacy:

- The proportion of patients in each study arm who achieved PASI 50/75/90 at weeks 4, 8 and 12 of treatment,
- The proportion of patients in each study arm who achieve an sPGA 0 or 1 at weeks 4, 8, and 12 relative to baseline,

Safety:

- The proportion of patients who developed SAEs,
- The proportion of patients who developed AEs,

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

[redacted]

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.

[redacted]

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.

[redacted]

[redacted]

[redacted]

8.4. The level of significance to be used

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

8.5. 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.

8.6. Statistical evaluations for the early study termination

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.