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Clinical Development

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CAIN457AKR04 / NCT05758402

A randomized, open, parallel, controlled, multi-center, interventional, cross-sectional study to evaluate the detection rate of psoriatic arthritis in Korean moderate-to-severe psoriasis patients, with or without Active Screening for Arthritis in Psoriasis (ASAP study)

Statistical Analysis Plan (SAP)

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15-Jun-2023	Before DB lock	--	N/A - First version	NA

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List of abbreviations

BMI	**Body mass index**
CASPAR	**Classification criteria for psoriatic arthritis**
CI	**Confidence interval**
CRF	**Case report form**
CRO	**Contract research organization**
DMARD	**Disease-modifying anti-rheumatic drug**
EARP	**Early arthritis for psoriatic patients**
eCRF	**Electronic case report form**
FAS	**Full analysis set**
MedDRA	**Medical dictionary for regulatory activities**
NAPSI	**Nail psoriasis severity index**
NPV	**Negative predictive value**
PASI	**Psoriasis area and severity index**
PPS	**Per protocol set**
PPV	**Positive predictive value**
PT	**Preferred term**
PsA	**Psoriatic arthritis**
PsO	**Psoriasis**
SAP	**Statistical analysis plan**
SJC	**Swollen joint count**
SOC	**System organ class**
TJC	**Tender joint count**
WHO	**World health organization**
WHO DD	**WHO drug dictionary**

1 Introduction

This Statistical Analysis Plan (SAP) is based on CAIN457AKR04 Protocol Version 1.0 dated 29Mar2022 and Case Report Form (CRF) Version 1.1 dated 08Jun2022 to provide a detailed description of the main features of the statistical analyses discussed in Section 12 of the Protocol, particularly, to present the endpoints and provide detailed information on the procedures and methods for their statistical analyses.

This SAP is to be finalized prior to data lock, and any changes made after its approval will be documented.

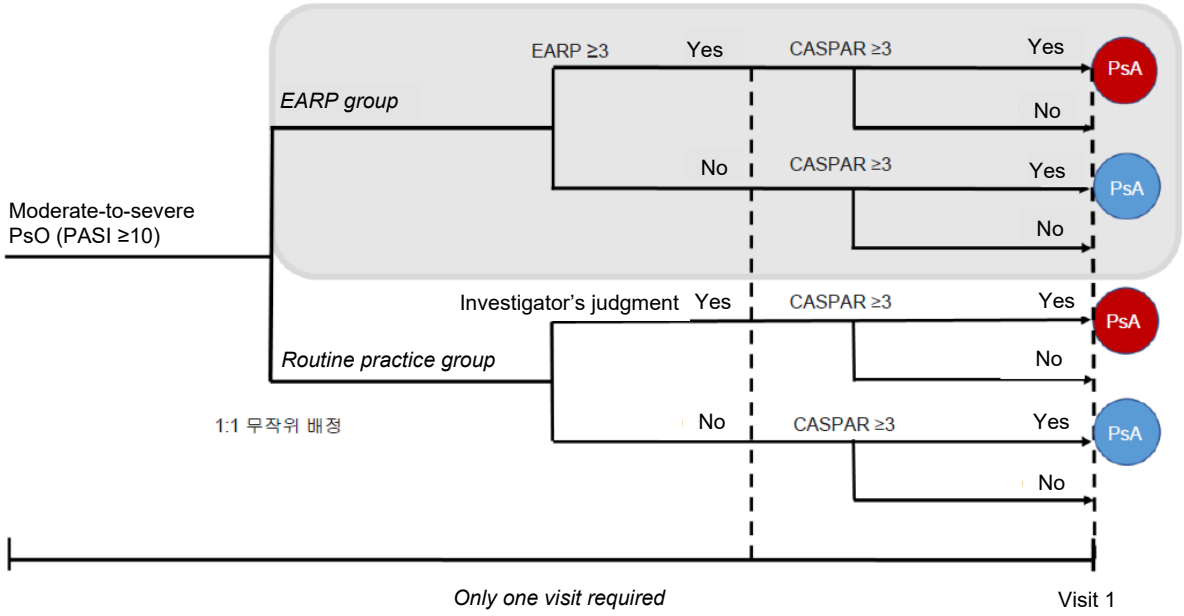
1.1 Study design

This is a randomized, open, parallel, controlled, multi-center, interventional, cross-sectional study to evaluate the detection rate of Psoriatic Arthritis (PsA) in Korean moderate to severe Psoriasis (PsO) patients with or without Early Arthritis for Psoriatic Patients (EARP) screening.

All procedures for each participant will be performed for one day. If an additional time is required depending on the circumstances of the institution and so on, the data specified in this study protocol are recommended to be collected as soon as possible. After the participants are enrolled in this study, they will be assessed whether they meet the inclusion/exclusion criteria. In terms of the severity of PsO, it will be assessed with the Psoriasis Area and Severity Index (PASI), and a score of 10 or higher is defined as moderate to severe PsO. A total 368 eligible participants will be randomized 1:1 into the EARP group and the Routine practice group.

For the EARP group, the investigator will ask the participants to complete the EARP questionnaire consisting of 10 questions. When the EARP score is ≥ 3, the participants will be suspected of having potential PsA. For the Routine practice group, the participants will be assessed by the investigator for potential PsA based on several clinical characteristics of the participants.

After the completion of the EARP questionnaire evaluation and the investigator's judgment as per routine practice in each group, all the participants will be evaluated using the Classification Criteria for Psoriatic Arthritis (CASPAR). Based on the CASPAR, participants with an inflammatory articular disease score of 3 or higher on the CASPAR are diagnosed with PsA, and the detection rate of PsA in each group is evaluated and compared.



1.2 Study objectives and endpoints

The objectives of this study and the related endpoints are as follows.

Table I Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for the primary objective(s)**
• To compare the detection rate of PsA with EARP screening versus detection rate of PsA without EARP screening in routine clinical practice in dermatological clinics amongst moderate to severe Korean PsO patients	• Detection rate of PsA
Secondary objective(s)	**Endpoint(s) for the secondary objective(s)**
• To compare the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) between EARP questionnaire (EARP group) and the investigator's judgment (Routine practice group)	• Sensitivity, specificity, PPV and NPV
• To describe the patient characteristics and disease severity between PsA and non-PsA patients	• Description of demographic characteristics, medications and PsO related characteristics

Detection rate of PsA is defined as the percentage of subjects with true positive results divided by all subjects in each EARP or Routine practice group (=TP/(TP+FP+TN+FN))

Sensitivity is defined as the percentage of subjects with true positive results divided by CASPAR score ≥ 3 subjects in each EARP or Routine Practice group (=TP/(TP+FN))

Specificity is defined as the percentage of subjects with true negative results divided by CASPAR score < 3 subjects in each EARP or Routine Practice group (=TN/(TN+FP))

PPV is defined as the percentage of subjects with true positive results divided by EARP ≥ 3 subjects in the EARP group and as the percentage of subjects with true positive results divided by subjects suspected of PsA by investigator's judgment in the Routine Practice group (=TP/(TP+FP))

NPV is defined as the percentage of subjects with true negative results divided by EARP < 3 subjects in the EARP group and as the percentage of subjects with true negative results divided by subjects not suspected of PSA by investigator's judgment in the Routine Practice group (=TN/(TN+FN))

True positive results are defined as subjects with CASPAR score ≥ 3 among subjects with EARP ≥ 3 in the EARP group and among those suspected of PsA by investigator's judgment in the Routine Practice group.

The true negative results are defined as subjects with CASPAR score < 3 among subjects with EARP < 3 in the EARP group and among those not suspected of PsA by investigator's judgment in the Routine Practice group (Table II).

Table II Evaluation outcomes

EARP group		
	CASPAR ≥ 3 (positive)	**CASPAR < 3 (negative)**
EARP ≥ 3 (positive)	TP (True Positive)	FP (False Positive)
EARP < 3 (negative)	FN (False Negative)	TN (True Negative)
Routine practice group		
	CASPAR ≥ 3 (positive)	**CASPAR < 3 (negative)**
Suspected of PsA by investigator's judgment (positive)	TP (True Positive)	FP (False Positive)
Not suspected of PsA by investigator's judgment (negative)	FN (False Negative)	TN (True Negative)

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by a designated Contract Research Organization (CRO) using the SAS software (Version 9.4).

Descriptive statistics will include the number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage of participants for categorical variables. If necessary, more detailed information will be provided.

For continuous data, statistical significance for differences between the two groups will be tested by Independent t-test if normality is met, or Wilcoxon rank sum test if normality is not met. For categorical data, statistical significance for differences between the two groups will be tested by Chi-square test. If cells with an expected frequency of <5 exceed 20% of all cells when testing for differences between the groups, Fisher's exact test will used instead of Chi-square test.

All the statistical tests will use a two-sided test at the significance level of 0.05. Statistical summaries will be presented to two decimal places, and p-values to three decimal places.

Prior/concomitant PsO related treatments and other medical history will be coded using the MedDRA (latest version at time of analysis) System Organ Class and Preferred Term and listed in descending order by incidence for the study groups. Prior/concomitant medications will be coded using the WHO Drug Dictionary (latest version at time of analysis) Therapeutic Main Group and Preferred Name and listed in descending order by incidence for the study groups.

Missing data will not be imputed, and all statistical analyses will be performed using available data.

2.1.1 General definitions

All procedures, including randomization of participants, and data collection are to be done at Visit 1, and baseline in this document refers to the data collected during Visit 1.

2.2 Analysis sets

The data obtained from this study will be analyzed for the full analysis set (FAS) and per-protocol set (PPS). The efficacy analysis will be performed using the FAS and PPS and the primary efficacy population is the FAS.

- The FAS will consist of randomized participants who had assessment for the primary endpoint.
- The PPS will consist of participants in the FAS who completed the study without major protocol deviations. Major protocol deviations include: PsA not evaluated by EARP or investigator, primary endpoint (CASPAR) not evaluated, deviation from the inclusion/exclusion criteria, randomization error, and other cases that could be considered major protocol deviations.

2.3 Patient disposition, demographics, and other baseline characteristics

2.3.1 Patient disposition

For randomized participants, the numbers and percentages of participants by randomization, whether PsA was evaluated by EARP or investigator, whether the study was completed, and the reason for not completing the study, will be presented by group and overall.

A separate list of participants who did not complete the study will be presented with the participant number, institution, group, sex, age, date of informed consent, and reason for study discontinuation.

Additionally, a separate list of screen failures will be presented with the participant number, institution, group, sex, age, date of informed consent, and reason for screen failure.

2.3.2 Protocol deviations and analysis restrictions

For randomized participants, the numbers and percentages of participants who had at least one major protocol deviation, both overall and for each category, will be presented by group and overall.

A separate list of participants with a major protocol deviation will be presented with the participant number, institution, group, sex, age, date of informed consent, whether the study was completed, and description of the major protocol deviation.

2.3.3 Disposition by analysis set

For randomized participants, the numbers and percentages of participants in the FAS and PPS and the reason for exclusion from the FAS and PPS will be presented by group and overall.

2.3.4 Demographics and other baseline characteristics

2.3.4.1 Demographic characteristics

Demographic characteristics will be analyzed for the FAS and will include the following parameters:

- Age (year): using the age data recorded in the CRF
- Age category (year): <65 years old, ≥65 years old
- Sex: Male, Female
- Height (cm)
- Weight (kg)
- Body mass index (BMI, kg/m^2): using the BMI data recorded in the CRF
- Drinking history: Current drinker, Former drinker, Never drinker
- Smoking history: Current smoker, Former smoker, Never smoker

Descriptive statistics will include the number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage of participants for categorical variables.

Statistical significance for differences between the two groups will be tested by Independent t-test or Wilcoxon rank sum test for continuous data, and by Chi-square test or Fisher's exact test for categorical variables.

2.3.4.2 PsO related characteristics

PsO related characteristics will be analyzed on the FAS and will include the following parameters:

- Duration of PsO (month): (date of informed consent - date of PsO diagnosis + 1) / 30.4375
  - If the month or day of PsO diagnosis is missing, January or day 1 will be imputed.
  - If the year of PsO diagnosis is missing, the date of diagnosis will be considered missing, as is the duration of disease, which will be therefore excluded from analysis.
- PASI score
- PASI categories: 10-20 (moderate), >20 (severe)
- PASI categories: 10-11, 12-13, 14-15, 16-17, 18-19, ≥20
- Family history of PsO: Present, Absent
  - The family history is 'Present' if any of the multiple selections (father, mother, siblings, and others) are checked, and 'Absent' if 'none' is checked.
- Types of PsO family history: Father, mother, siblings, others
  - Participants with 'Present' for PsO family history will be analyzed; the multiple selections allow for multiple counting.
- Family history of PsA: Present, Absent
  - 'Present' if any of the multiple selections (father, mother, siblings, and others) are checked, and 'Absent' if 'none' is checked
- Types of PsA family history: Father, mother, siblings, others
  - Participants with 'Present' for PsA family history will be analyzed; the multiple selections allow for multiple counting.
- Presence or absence of hard-to-treat area involvement: Present, Absent
  - 'Present' if any of the multiple selections for hard-to-treat area involvement (scalp, palmoplantar, and nails) are checked, and 'Absent' if 'none' is checked
- Hard-to-treat area involvement: Scalp, palmoplantar, and nails

  - Participants with 'Present' for hard-to-treat area involvement will be analyzed; the multiple selections allow for multiple counting.
- Musculoskeletal symptoms: Present, Absent
- Nail psoriasis severity index (NAPSI): Scores for each of the left and right hands and left and right feet and their total score
- Number of swollen joints (SJC66)
- Number of tender joints (TJC68)
- Sum of SJC66 and TJC68

Descriptive statistics will include the number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage of participants for categorical variables.

Statistical significance for differences between the two groups will be tested by Independent t-test or Wilcoxon rank sum test for continuous data, and by Chi-square test or Fisher's exact test for categorical variables.

2.3.4.3 Medical history

Medical history will be analyzed on the FAS.

The respective history of heart disease, stroke, diabetes, hyperlipidemia, hypertension, and fatty liver will be analyzed in categories of medical history, current medical condition, and none as follows:

- Past medical history: The disease is 'Present' and not 'Ongoing'
- Current medical condition: The disease is 'Present' and 'Ongoing'
- None: The disease is 'Absent'

The number and percentage of participants with each medical history will be presented by group and overall; statistical significance for differences between the groups will be tested by Chi-square test or Fisher's exact test.

Other medical history, including all medical history collected in the 'Other medical history' eCRF page, will be analyzed in categories of past medical history and current medical condition as follows:

- Past medical history: The disease is not 'Ongoing'
- Current medical condition: The disease is 'Ongoing'

For past medical history and current medical conditions, the number and percentage of participants with at least one medical history overall and in each SOC and PT of MedDRA will be presented by group and overall.

2.3.4.4 Medications

Medications will be analyzed on the FAS; prior and concomitant medications, including all medications collected in the 'prior/concomitant medications' eCRF page, will be analyzed in categories as follows:

- Prior medication: The medication is not 'Ongoing'
- Concomitant medication: The medication is 'Ongoing'

For prior and concomitant medications, the number and percentage of participants having at least one medication overall and in each WHO DD Therapeutic Main Group and Preferred Name will be presented by group and overall.

2.3.4.5 PsO related treatment other than medication

Prior/concomitant PsO related treatments other than medications will be analyzed for the FAS; prior and concomitant treatments, including all treatments collected in the 'Prior/concomitant PsO related treatments' eCRF page, will be analyzed in categories as follows:

- Prior PsO related treatment other than medication: The treatment is not 'Ongoing'
- Concomitant PsO related treatment other than medication: The treatment is 'Ongoing'

For prior and concomitant PsO related treatments, the number and percentage of participants with at least one treatment overall and in each SOC and PT of MedDRA will be presented by group and overall.

2.4 Analysis supporting primary objective(s)

The primary objective of this study is to compare the detection rate of PsA in patients with moderate-to-severe PsO between the EARP group and the Routine practice group.

2.4.1 Primary endpoint(s)

The primary endpoint of the study is the detection rate of PsA. Detection rate of PsA is defined as the percentage of subjects with true positive results divided by all subjects in each EARP or Routine practice group.

True positive results of PsA detection rate are defined as subjects with CASPAR score ≥ 3 among subjects with EARP ≥ 3 in the EARP group and among those suspected of PsA by investigator's judgment in the Routine Practice group.

2.4.2 Statistical hypothesis, model, and method of analysis

To compare PsA detection rates between the EARP group and the Routine practice group, the following hypothesis will be tested at a two-sided 0.05 level.

$$H_0: P_I = P_C \; vs. \; H_a: P_I \neq P_C$$

where P_I and P_C are the detection rate of PsA in the EARP group and the Routine practice group, respectively.

The number of participants with true positive and the detection rate of PsA will be presented by each group using the FAS. The point-estimate of the difference in detection rate between the two groups (EARP group – Routine practice group) will be given with its two-sided 95% Confidence Interval (CI) and the p-value for the null hypothesis. If the lower limit of the two-sided 95% CI of the difference between the two groups is greater than 0, the EARP group is deemed superior to the Routine practice group.

2.4.3 Supplementary analyses

The same analyses for the FAS will be conducted for the PPS for the primary efficacy endpoint, and the results will be presented.

2.5 Analysis supporting secondary objectives

2.5.1 Sensitivity, specificity, PPV and NPV

Analyses for sensitivity, specificity, PPV and NPV will be performed on the FAS and PPS.

Sensitivity will be summarized with the number and percentage of participants who have true positive (TP) among those who have true positive (TP) and false negative (FN), and the statistical significance of the difference between the two groups will be tested using Chi-square test or Fisher's exact test.

Specificity will be summarized with the number and percentage of participants who have true negative (TN) among those who have true negative (TN) and false positive (FP), and the statistical significance of the difference between the two groups will be tested using Chi-square test or Fisher's exact test.

Positive predictive value will be summarized with the number and percentage of participants who have true positive (TP) among those who have true positive (TP) and false positive (FP), and the statistical significance of the difference between the two groups will be tested using Chi-square test or Fisher's exact test.

Negative predictive value will be summarized with the number and percentage of participants who have true negative (TN) among those who have true negative (TN) and false negative (FN), and the statistical significance of the difference between the two groups will be tested using Chi-square test or Fisher's exact test.

2.5.2 Demographic characteristics and PsO related characteristics with or without PsA

Demographic and PsO related characteristics by the presence or absence of PsA will be analyzed on the FAS and PPS. The presence or absence of PsA is defined as below:

- PsA present: PsA diagnosis result is true positive
- PsA absent: PsA diagnosis result is false positive, true negative, or false negative

2.5.2.1 Demographic characteristics with or without PsA

The parameters for demographic characteristics are identical to the parameters provided in Section 2.3.4.1.

Descriptive statistics will include the number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage of participants for categorical variables, presented by the presence or absence of PsA.

Statistical significance for differences between the two groups will be tested by Independent t-test or Wilcoxon rank sum test for continuous data, and by Chi-square test or Fisher's exact test for categorical variables.

2.5.2.2 PsO related characteristics with or without PsA

The parameters for PsO related characteristics are identical to the parameters provided in Section 2.3.4.2.

Descriptive statistics will include the number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage of participants for categorical variables, presented by the presence or absence of PsA.

Statistical significance for differences between the two groups will be tested by Independent t-test or Wilcoxon rank sum test for continuous data, and by Chi-square test or Fisher's exact test for categorical variables.

2.5.2.3 Medical history with or without PsA

The definitions of medical history and other history are identical to the definitions provided in Section 2.3.4.3.

For medical history, the number and percentage of participants in each category will be presented by the presence or absence of PsA, and the statistical significance of the difference between those with and without PsA will be tested using Chi-square test or Fisher's exact test.

For other past medical history and current medical conditions, the number and percentage of participants with at least one medical history overall and in each SOC and PT of MedDRA will be presented by the presence or absence of PsA.

2.5.2.4 Medications with or without PsA

The definitions of prior and concomitant medications are identical to the definitions provided in Section 2.3.4.4.

For prior and concomitant medications, the number and percentage of participants having at least one medication overall and in each WHO DD Therapeutic Main Group and Preferred Name will be presented by the presence or absence of PsA.

2.5.2.5 PsO related treatment other than medication with or without PsA

The definitions of prior and concomitant PsO related treatments other than medication are identical to the definitions provided in Section 2.3.4.5.

For prior and concomitant PsO related treatments other than medication, the number and percentage of participants with at least one treatment overall and in each SOC and PT of MedDRA will be presented by the presence or absence of PsA.

[redacted]

2.7 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

According to previous studies, the prevalence of PsA among PsO patients in Korea ranged from 9.0% to 14.1% (9.0% in Back HJ, et al. 2000, 10.8% in Oh et al. 2017, 13.5% in Choi et al. 2017, 14.1% in Choi HJ, et al. 2008) (Back HJ, et al. 2000) (Oh EH, et al. 2017) (Choi JW, et al. 2017) (Choi HJ, et al. 2008). Considering that this study excludes patients who have received treatment with biologic disease-modifying anti-rheumatic drugs (DMARDs) to reduce the effect of any confounding factors as trying to demonstrate the usefulness of the EARP as an

early diagnosis tool for PsA, the detection rate of PsA among patients with PsO is assumed to be 9% in the Routine practice group.

For the EARP group, the detection rate of PsA among PsO patients is assumed to be 19.7%, given that in a recent large meta-analysis of 266 studies worldwide, the overall prevalence of PsA among PsO patients was reported as 19.7% (Alinaghi F, et al. 2019). Several studies and meta-analyses revealed that undiagnosed PsA is common in patients with PsO, ranging from 9% to 13.76% (9% in Sleman et al. 2015, 10.1% in Coates et al. 2016, 12.4% in Mease et al. 2013, 13.76% in Alshaikh et al. 2020) (Spelman L, et al. 2015) (Coates LC, et al. 2016b) (Mease PJ, et al. 2017) (Alshaikh AF, et al. 2020). Thus, it would be a reasonable assumption that the detection rate of PsA among patients with PsO will increase to 19.7% in the EARP group if the EARP screening will improve the detection rate by around 11%.

Based on a two-sided α=0.05 and power 1-β=0.80, assuming the PsA detection rates of 9% and 19.7% in the Routine practice and EARP groups, respectively, the sample size of this study is estimated to be approximately 165 per group.

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 (P_C * (1 - P_C) + P_I * (1 - P_I))}{(P_C - P_I)^2} = \frac{(1.96 + 0.842)^2 (0.09 * (1 - 0.09) + 0.197 * (1 - 0.197))}{(0.09 - 0.197)^2} = 164.64$$

Considering 10% of invalid cases, a total of 368 patients (184 patients per group) is planned to be enrolled in this study.

4 Change to protocol specified analyses

No analyses changed from the protocol.

5 Reference

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