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Clinical Trial Protocol 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)

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List of abbreviations

BMI	**Body mass index**
CASPAR	**Classification criteria for psoriatic arthritis**
CI	**Confidence interval**
CRO	**Contract research organization**
CTT	**Clinical trial team**
DMARD	**Disease-modifying anti-rheumatic drug**
EARP	**Early arthritis for psoriatic patients**
eCRF	**Electronic case report form**
EDC	**Electronic data capture**
FAS	**Full analysis set**
GCP	**Good clinical practice**
GRAPPA	**Group for research and assessment of psoriasis and psoriatic arthritis**
ICF	**Informed consent form**
ICH	**International council for harmonization of technical requirements for pharmaceuticals for human use**
IRB	**Institutional review board**
IWRS	**Interactive web response system**
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**
PsA	**Psoriatic arthritis**
PsO	**Psoriasis**
QMS	**Quality management system**
SJC	**Swollen joint count**
SLE	**Systemic lupus erythematosus**
SOP	**Standard operating procedure**
TJC	**Tender joint count**
WHO	**World health organization**

Glossary of terms

Assessment	**A procedure used to generate data required by the study**
Clinical Trial Team	**A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.**
Coded Data	**Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.**
Electronic Data Capture (EDC)	**Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care**
Enrollment	**Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants**
Participant	**A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection**
Participant number	**A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.**
Personal data	**Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.**
Randomization	**The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.**
Randomization number	**A unique identifier assigned to each randomized participant**
Screen Failure	**A participant who did not meet one or more criteria that were required for participation in the study**
Source Data/Document	**Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource**
Variable (or endpoint)	**The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.**

Protocol summary

Protocol number	CAIN457AKR04
Full Title	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 **A**ctive **S**creening for **A**rthritis in **P**soriasis (ASAP study)
Brief title	Detection rate of psoriatic arthritis in Korean moderate-to-severe psoriasis patients, with or without **A**ctive **S**creening for **A**rthritis in **P**soriasis (ASAP study)
Sponsor and Clinical Phase	Sponsor - Novartis / Clinical phase - Not applicable
Investigation type	Other (Cross-sectional study)
Study type	Interventional
Purpose	To confirm that the Early Arthritis for Psoriatic Patients (EARP) screening is effective in the early diagnosis of Psoriatic Arthritis (PsA)
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 Psoriasis (PsO) patients Endpoint: • Detection rate of PsA
Secondary Objectives	To compare the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) between EARP questionnaire (EARP group) and the investigator's judgement (Routine practice group) To describe the patient characteristics and disease severity between PsA and non-PsA patients Endpoint: • Sensitivity, specificity, PPV and NPV • Description of demographic characteristics, medications and PsO related characteristics
Study design	This is a randomized, open, parallel, controlled, multi-center, interventional, cross-sectional study to evaluate the detection rate of PsA in Korean moderate to severe PsO patients with or without EARP screening. The participants will be randomized into the EARP group and the Routine practice groups. The detection rate of PsA in each group is evaluated and compared.
Study population	A total of 368 participants who are male and female moderate to severe PsO patients aged 19 years or older.
Inclusion criteria	1. Patient who is ≥ 19 years of age at the time of study enrollment 2. Patient who had an established diagnosis of PsO based upon clinical evidence and documented medical history

	3. Patient who is moderate to severe PsO (Psoriasis Area and Severity Index (PASI) score ≥ 10) 4. Patient who is willing and able to comply with study procedures 5. Patient who is able to provide the informed consent form (ICF)
Exclusion criteria	1. Patients who have formal pre-existing diagnosis of PsA 2. Patients who have ever received treatment with biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) 3. Patients who currently receive systemic glucocorticoids 4. Patients who currently receive opioid analgesics 5. Patients who has other known pre-existing dermatological or rheumatological diseases - Non-plaque psoriasis - Rheumatoid arthritis - Osteoarthritis - Gout - Reactive arthritis - Ankylosing spondylitis - Axial spondyloarthritis - Enteropathic arthritis - Plantar fasciitis - Systemic lupus erythematosus (SLE) 6. Female patients who are pregnant 7. Patients who are participating in other interventional clinical trials 8. Patients who have already had PsA screening via screening questionnaires or imaging
Study Intervention	Screening tool: the EARP questionnaire
Efficacy assessments	Primary endpoint: • Detection rate of PsA Secondary endpoint: • Sensitivity, specificity, PPV and NPV • Demographic characteristics • Medications • PsO related characteristics - PsO related medical history - Co-morbidities - Nail Psoriasis Severity Index (NAPSI) - SJC66/TJC68

Safety assessments	Not applicable as no drug is involved.
Data analysis	The primary objective of this study is to demonstrate that the EARP screening is effective in the early diagnosis of PsA. 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 percentage of patients with PsA in each EARP group and Routine practice groups, respectively. The number and percentage of PsA confirmed by the CASPAR criteria for each group are presented and the point-estimate for the difference of the proportion between two groups will be given with its two-sided 95% Confidence Interval (CI) and the p-value for the null hypothesis. Analysis on sensitivity, specificity, PPV and NPV will be presented by EARP group and Routine practice group. Analysis on the demographic characteristics and PsO related characteristics will be presented by patients with and without PsA. Descriptive statistics will be summarized with the number of patients, mean, standard deviation, median, minimum, and maximum for the continuous variables and with the number and percentage of patients for the categorical variables. The statistical significance for the differences between two groups is tested using independent t-test or Wilcoxon rank sum test for continuous data and using Chi-square test or Fisher's exact test for the categorical data.
Key words	Psoriasis, Psoriatic arthritis, Risk, Screening-tools, EARP

1 Introduction

1.1 Background

Psoriatic Arthritis (PsA) is chronic, inflammatory, musculoskeletal disease associated with Psoriasis (PsO) (Ritchlin CT, et al. 2017). According to previous studies, between 30% to 41% of patients with PsO develop PsA over the course of their lifetime (Haroon M, et al. 2014) (Philip J, et al. 2013). Musculoskeletal manifestations of PsA include peripheral arthritis, spondylitis, dactylitis and enthesitis (Ogdie A, et al. 2020). Skin manifestations of PsA include PsO and nail disease (Ogdie A, et al. 2020). Beyond the musculoskeletal and skin features, patients with PsA experience fatigue, physical function limitations, sleep disturbance, as well as diminished work capacity and social participation (Orbai AM, et al. 2017).

The 2015 treatment recommendations of Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) highlight the importance of early diagnosis of PsA as one of the six final overarching principles for the care of patients with PsA (Coates LC, et al. 2016a). Delayed diagnosis of PsA may result in joint destruction and permanent disabilities, whereas early diagnosis and prompt therapy could prevent this irreversible joint damage (Tinazzi I, et al. 2012). Several studies conducted on the benefits of early diagnosis of PsA have shown that treatment of early stage progressive PsA can substantially improve the long-term prognosis (McLaughlin M, et al. 2014) (Theander E, et al. 2014).

In Korea, the reported prevalence of PsA in PsO patients ranges from 9 to 14.1%, which is significantly different from the prevalence in previous studies (Choe YB, et al. 2019). This may be due to genetic differences, but may also be due to inadequate screening and diagnosis of PsA among PsO patients in Korea (Shin D, et al. 2016).

The Classification Criteria for Psoriatic Arthritis (CASPAR) were developed by an international group of rheumatologists in 2006 to help standardize the diagnosis of PsA. These classification criteria consist of two groupings: the stem (or required criteria) consist of inflammatory joint (peripheral) disease, enthesitis, and inflammatory axial disease and criteria is associated with a numerical value (Mease PJ, et al. 2014) (Taylor W, et al. 2006). To fulfill the CASPAR criteria, a patient must present with at least one of the stem components and get 3 points or higher from the criteria. The criteria include clinical assessment (current PsO or a personal/family history of PsO, psoriatic nail dystrophy, and current dactylitis or history of dactylitis), radiography (juxta-articular new-bone formation), and blood test (negative test result for the presence of rheumatoid factor). Since skin lesions classically precede joint symptoms, dermatologists are in ideal position to play a key role in identifying patients at risk for PsA before irreversible joint damage occurs (Busse K, et al. 2010) (Belinchón I, et al. 2020). However, the CASPAR criteria are not usually performed routinely in dermatology clinics, so the diagnosis of PsA in PsO patients can sometimes be overlooked. Therefore, it seems as though there is a need for a simple tool that could assist early and active diagnosis of PsA in dermatology.

There are several screening tools for PsA; the Psoriasis Epidemiology Screening Tool (PEST), the Psoriatic Arthritis Screening and Evaluation (PASE) and the Early Arthritis for Psoriatic Patients (EARP) questionnaire. These follow a similar questionnaire structure and have all been validated in patients with PsO. Among these, the EARP questionnaire is a simple, user-friendly and easy to administer screening tool. And it focuses on early diagnosis of PsA and has a higher

sensitivity than the PASE and PEST questionnaires (Iragorri N, et al. 2018). Thus, the EARP questionnaire could assist dermatologists in screening of the potential PsA patients and make early diagnosis of PsA. Also, there are studies which have shown that the detection rate of PsA can be improved via active screening of PsO patients (Mahmood F, et al. 2017).

These background information suggest the potential benefit of using EARP questionnaire as a screening tool for PsA in everyday dermatology practice. Therefore, it will be helpful to perform a clinical trial to compare the rate of PsA diagnosis from the current routine dermatology practice in Korea and that from active utilization of PsA screening tool, the EARP.

1.2 Purpose

Delays in diagnosis of PsA can lead to irreversible joint damage, therefore early detection of PsA through active screening of arthritis symptoms in PsO patients can be beneficial. The EARP is a simple and easy-to-use screening tool which can be utilized in a real-world setting of dermatology practice, and it is focused on early diagnosis of PsA. The purpose of this study is to confirm that the EARP screening is effective in early diagnosis of PsA.

2 Objectives and endpoints

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

Table 2–1 Objectives and related endpoints

Objective(s)	Endpoint(s)
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	**Endpoint(s) for primary objective(s)** • Detection rate of PsA
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 judgement (Routine practice group) • To describe the patient characteristics and disease severity between PsA and non-PsA patients	**Endpoint(s) for secondary objective(s)** • Sensitivity, specificity, PPV and NPV • Description of demographic characteristics, medications and PsO related characteristics

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

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

The true positive results are defined as subjects with CASPAR score ≥ 3 among EARP ≥ 3 for the EARP group and among those suspected of PsA by investigator's judgement for the Routine Practice group.

The true negative results are defined as subjects with CASPAR score < 3 among EARP < 3 for the EARP group and among those not suspected of PsA by investigator's judgement for the Routine Practice group (Table 2-2).

Table 2–2 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 judgement (positive)	TP (True Positive)	FP (False Positive)
Not suspected of PsA by investigator's judgement (negative)	FN (False Negative)	TN (True Negative)

3 Study design

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

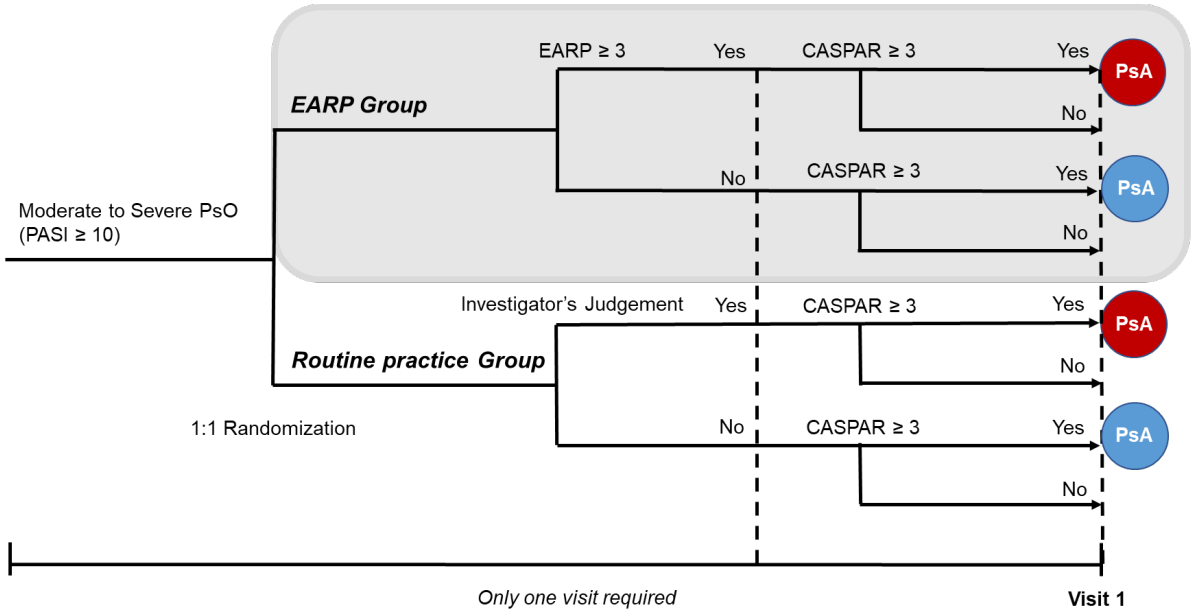
All procedures for each patient will be performed for one day. If an additional time is required depending on the circumstances of the institution and so on, the data specified in this study protocol are recommended to be collected as soon as possible. After the participants are enrolled in this study, 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 if the 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 groups.

For the EARP group, the investigator will ask the participants about the EARP questionnaire consisting of 10 questions. When the EARP score ≥ 3, the participants will be suspected for having potential PsA. For Routine practice group, the investigator will select the participants suspected of PsA in consideration of the various clinical characteristics of the participants.

After the completion of EARP questionnaire evaluation and the investigator's judgement as per routine practice in each group, all the participants will be evaluated using CASPAR. According to the CASPAR, participants who have inflammatory articular disease with 3 or more points from the CASPAR are diagnosed as PsA, and the detection rate of PsA in each group is evaluated and compared.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This is a randomized, open, parallel, controlled, multi-center, interventional, cross-sectional study to evaluate the detection rate of PsA in Korean moderate-to-severe PsO patients, with or without active screening for arthritis in PsO.

The EARP questionnaire, an intervention in this study, is used for early diagnosis of PsA. In order to evaluate the usefulness of early diagnosis of PsA through the EARP questionnaire, the control group is designed to screen subjects suspected of have PsA according to the routine practice of real-world dermatology setting. According to the characteristics of the intervention used for early diagnosis of PsA in each group, this study is designed as an open study. Therefore,

1:1 balanced randomization is planned to compensate for the limitation of the open study and to reduce the bias.

Regarding the study population, this study will include male and female patients with moderate to severe PsO. It is confirmed that the PASI score, which evaluates the severity of PsO, was significantly higher in PsO patients with PsA than in PsO patients without PsA. This means that there is a close relation between the severity of PsO and the prevalence of PsA (Choi JW, et al. 2017). Therefore, in order to conduct the study on patients expected to have a high prevalence of PsA, patients with a PASI score of 10 or higher, defined as moderate to severe PsO patients, are selected as a study population. In addition, this study excluded patients who has ever received the biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) which may mask symptoms of PsA and thus make PsA more difficult to be diagnosed in PsO patients. By excluding these patients, the effect of the questionnaire can be confirmed more clearly in the real-world setting.

4.2 Rationale for Intervention

According to the 2015 treatment recommendation of GRAPPA, the importance of early diagnosis of PsA is emphasized as one of the six final overarching principles for prognosis of PsA (Coates LC, et al. 2016a). However, the precise investigation such as radiography and rheumatoid factor are required for PsA diagnosis, and this interrupts the early diagnosis of PsA. Furthermore, unlike early rheumatoid arthritis where the majority of cases have anti-citrullinated protein autoantibodies, a specific marker is absent in early PsA. Therefore, there is a greater reliance on clinical assessments in at-risk groups (Jo SJ et al. 2019), and the need for a screening tool of questionnaire has emerged.

As mentioned above, a various tool has been developed to screen or diagnose PsA in PsO patients and the EARP questionnaire is a simple, user-friendly and easy to administer screening tool that can be easily used in dermatology. Furthermore, it focuses on early diagnosis of PsA and has a higher sensitivity than the PASE and PEST questionnaires (Iragorri N, et al. 2018).

Therefore, the EARP screening is selected as an intervention because it is considered to be the most applicable screening tool in the real-world dermatology setting in Korea, and it is thought that it will result in high early diagnosis rate of PsA.

4.3 Rationale for choice of control group

In this study, the control group is the routine practice group where the PsA screening gets done via clinical suspicion of the investigator.

Typically, patients do not know about the connection between PsO and PsA. Thus, patients generally do not inform dermatologists about their PsA symptoms, and often the symptoms of PsA are in the early stage which makes PsA difficult to be recognized by the patients. Therefore, in routine dermatology practice, PsO patients may get delayed with diagnosis of PsA until they develop obvious joint symptoms. With regards to treatment, some dermatologists refer the patients to rheumatologists when the patients get noticeable joint symptoms (Jo SJ, et al. 2019). However, there are some dermatologists who treat the PsA patients themselves especially those in the early stage of the disease.

Therefore, we intend to establish the validity of the EARP screening by comparing the PsA diagnosis rate in routine dermatological practice and in the EARP screening.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable

4.5 Risks and benefits

Not applicable

4.6 Rationale for Public Health Emergency mitigation procedures

Not applicable

5 Study Population

The study will include male and female patients with moderate to severe PsO. A total of 368 patients (184 in each treatment arm) will be randomized at 15 centers across the Korea (Depending on the progress of the study, additional sites may be added.).

The calculation of the sample size is provided in Section 12.8.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Patient who is ≥ 19 years of age at the time of study enrollment
2. Patient who had an established diagnosis of PsO based upon clinical evidence and documented medical history
3. Patient who is moderate to severe PsO (PASI score ≥ 10)
4. Patient who is willing and able to comply with study procedures
5. Patient who is able to provide the informed consent form (ICF)

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are **not** eligible for inclusion in this study.

1. Patients who have formal pre-existing diagnosis of PsA
2. Patients who have ever received treatment with biologic DMARDs
3. Patients who currently receive systemic glucocorticoids.
4. Patients who currently receive opioid analgesics
5. Patients who have other known pre-existing dermatological or rheumatological diseases
    - Non-plaque psoriasis
    - Rheumatoid arthritis
    - Osteoarthritis
    - Gout
    - Reactive arthritis
    - Ankylosing spondylitis

- Axial spondyloarthritis
- Enteropathic arthritis
- Plantar fasciitis
- Systemic lupus erythematosus (SLE)

6. Female patients who are pregnant
7. Patients who are participating in other interventional clinical trials
8. Patients who have already had PsA screening via screening questionnaires or imaging.

6 Study Intervention

6.1 Study Intervention

6.1.1 EARP group

The EARP questionnaire will be provided to the investigator in a Korean translated form. For the EARP group, the investigator provides this questionnaire to the participants, who will fill out this according to their symptoms. The investigator should calculate the total score of the questionnaire answered by the participant. After the completion of EARP questionnaire evaluation, the participants will be evaluated using the CASPAR.

6.1.2 Routine practice group

In the control group, PsA risk will be assessed in moderate to severe PsO patients as per routine practice without using the EARP screening. Routine practice for the treatment of moderate to severe PsO patients seldom include active screening for symptoms of PsA using any screening questionnaires. Instead of that, the investigator may ask the participants if they have any joint pain currently or in the past. After the completion of PsA risk assessment via routine practice according to the investigator's judgement, the participants will be evaluated using the CASPAR.

6.2 Participant numbering, randomization

6.2.1 Participant numbering

Each participant is identified in the study by a participant number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the study. The Participant No. consists of the site number (as assigned by Novartis to the investigative site) with a sequence number suffixed to it, so that each participant's participation is numbered uniquely across the entire database.

6.2.2 Randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased.

Participants who meet all inclusion criteria and none of the exclusion criteria will be centrally, randomly allocated with a 1:1 ratio to either the EARP group or the Routine practice group using an Interactive Web Response System (IWRS).

The Randomization Number (Randomization No.) consists of the group number and a sequence number. An eligible patient will be given the lowest available sequence number. This number assigns the patient to one of the groups.

Randomization will be stratified by the site in order to minimize the bias caused by each judgment of investigator.

6.3 Blinding

Assigned group will be open to participants, investigator staff, persons performing the assessments and the Novartis clinical trial team (CTT). Such that no aggregate statistical analyses by treatment shall be performed prior to the database lock.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)-approved informed consent.

In cases where the participant's representative(s) gives consent, the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will review the Contract Research Organization (CRO) proposed ICF to ensure it complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB.

8 Visit schedule and assessments

The assessment schedule (Table 8–1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant’s source documentation.

All baseline assessments may occur during the screening, and all procedures for each participant is performed for one day (Visit 1). 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.

Participants should be seen for all assessments as outlined in the assessment schedule (Table 8–1).

Table 8–1 Assessment schedule

Period		**Screening**	**Randomization**	**Intervention**	**Physical examination**	**Evaluation**
Visit Name		**Visit 1**				
Day/Week/Month		**Day 1**				
Obtain informed consent [1)]		X				
Demographics	Year of birth, age	X				
	Sex	X				
	Height (cm)	X				
	Weight (kg)	X				
	Body Mass Index (BMI)	X				
	Alcohol consumption status	X				
	Smoking status	X				
Pregnancy tests [2)]		X				
Inclusion/exclusion criteria		X				
Medical history and medication [3)]	Medical history	X				
	PsO related medical history	X				
	Medications	X				
	PsO related treatment other than medications	X				
Randomization			X			
Intervention	EARP screening (EAPR group)			X		
	Investigator's judgement (Routine practice group)			X		
Physical examination	NAPSI				X	
	SJC66				X	
	TJC68				X	

Period		**Screening**	**Randomization**	**Intervention**	**Physical examination**	**Evaluation**
Visit Name		**Visit 1**				
Day/Week/Month		**Day 1**				
CASPAR [4)]	Clinical assessment					X
	Blood test					X
	Radiography					X

PsO; Psoriasis; EARP: Early arthritis for psoriatic patients; NAPSI: Nail psoriasis severity index; SJC: Swollen joint count; TJC: Tender joint count; CASPAR: Classification criteria for psoriatic arthritis; PsA: Psoriatic arthritis

1) All procedures must be conducted after getting ICF, and participant numbers are assigned in the order of consent.
2) For all female patients of child bearing potential only, a urine-HCG test will be performed.
3) **Medical history and medication**
   - Medical history: Heart diseases, stroke, diabetes, hyperlipidemia, hypertension, fatty liver and other diseases
   - PsO related medical history: Date of diagnosis for PsO, family history of PsO, family history of PsA, PASI score, hard-to-treat area involvement (scalp, palmoplantar and nails), musculoskeletal symptoms
   - Medications
   - PsO related treatment other than medications
4) **CASPAR:** Based on the CASPAR, participants are diagnosed with or without PsA.
   - Clinical assessment: Inflammatory articular disease (inflammatory joint (peripheral) disease, enthesitis, and inflammatory axial disease), date of diagnosis for PsO#, family history of PsO#, presence or absence of typical psoriatic nail dystrophy (onycholysis, pitting, hyperkeratosis), presence or absence of dactylitis, history of dactylitis (recorded by rheumatologist)
   - Blood test: Rheumatoid factor
   - Radiography: Hand and foot plain X-ray (evidence of juxta-articular new bone formation in hand (including wrist) and feet (including ankle))

   Note) #: These values which are included the CASPAR are replaced by the values in Section 8.2.2.2.

8.1 Screening

All procedures must be conducted after getting ICF, and participant numbers are assigned in the order of consent. Screening is performed to assess inclusion/exclusion criteria (Refer to the value of Section 8.2).

8.1.1 Information to be collected on screening failures

Participants who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the electronic case report form (eCRF). The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure participants.

Participants who are randomized and fail to start study (e.g., participants randomized in error) will be considered an early terminator. The reason for early termination should be recorded on the eCRF.

8.2 Participant demographics/other baseline characteristics

The following patient demographic and other baseline characteristics data will be collected on all participants.

8.2.1 Demographic characteristics

The following information will be collected/documented at screening for each patient:

- Year of birth
- Age
- Sex
- Height (cm)
- Weight (kg)
- BMI
- Alcohol consumption status (current drinker, past-drinker or non-drinker)
- Smoking status (current smoker, ex-smoker or never smoked)

8.2.2 Medical history and medication

8.2.2.1 Medical history

- Heart diseases (presence or absence/start date/end date/ongoing or not)
- Stroke (presence or absence/start date/end date/ongoing or not)
- Diabetes (presence or absence/start date/end date/ongoing or not)
- Hyperlipidemia (presence or absence/start date/end date/ongoing or not)
- Hypertension (presence or absence/start date/end date/ongoing or not)

- Fatty liver (presence or absence/start date/end date/ongoing or not)
- Other diseases (presence or absence/disease name/start date/end date/ongoing or not)

8.2.2.2 PsO related medical history

- Date of diagnosis for PsO
- Family history of PsO
- Family history of PsA
- PASI score
- Hard-to-treat area involvement (presence or absence of scalp, palmoplantar and nails)
- Musculoskeletal symptoms (presence or absence/site)

8.2.2.3 Medications

- Presence or absence of medications
- Drug name
- Daily dose
- Route of administration
- Administration period (start date/end date/ongoing or not)
- Purpose of administration (PsO related/others)

8.2.2.4 PsO related treatment other than medications

- Presence or absence of PsO related treatment
- Treatment name
- Treatment period (start date/end date/ongoing or not)

8.3 EARP

The EARP is a questionnaire composed of ten questions regarding symptoms of joint disease, developed for the early diagnosis of PsO. This questionnaire consists of simple questions, and it has 0-10 range (Tinazzi I, et al. 2012).

In this study, the EARP screening is only conducted on the EARP group, and when the EARP score ≥ 3, it can be judged that the patients is potential PsA. The Korean EARP questionnaire is included in Appendix 1. EARP questionnaire.

- EARP score

8.4 Physical examinations

8.4.1 NAPSI

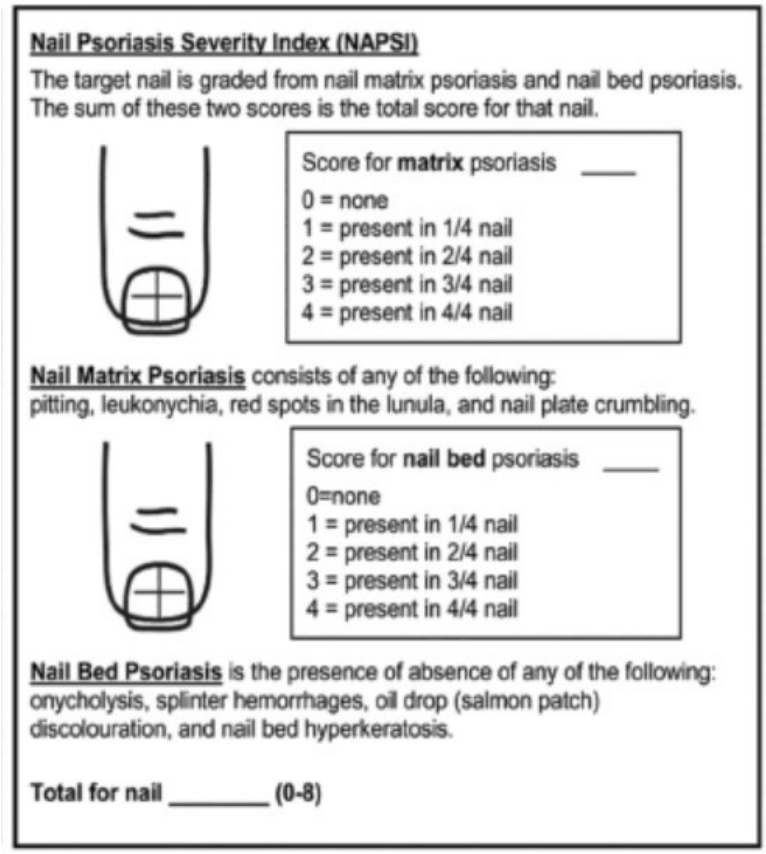
The nails will be visually inspected, and if an abnormality is observed, a photograph will be obtained and will be evaluated by investigator using NAPSI.

NAPSI is a numeric, reproducible, objective, simple tool for evaluation of nail PsO. This scale is used to evaluate the severity of nail bed PsO and nail matrix PsO by area of involvement in the nail unit. The nail is divided with imaginary horizontal and longitudinal lines into quadrants. Each nail is given a score for nail bed PsO (0-4) and nail matrix PsO (0-4) depending on the presence of any of the features of nail PsO in that quadrant (Rich P, et al. 2003). A total score per nail is 0-8, and the range of the total scores from all nails is 0-160 (toenails are included).

In this study, NAPSI is measured for all participants.

- Score of left hand
- Score of right hand
- Score of left foot
- Score of right foot
- Total score

Figure 8-1 NAPSI score



8.4.2 SJC66/TJC68

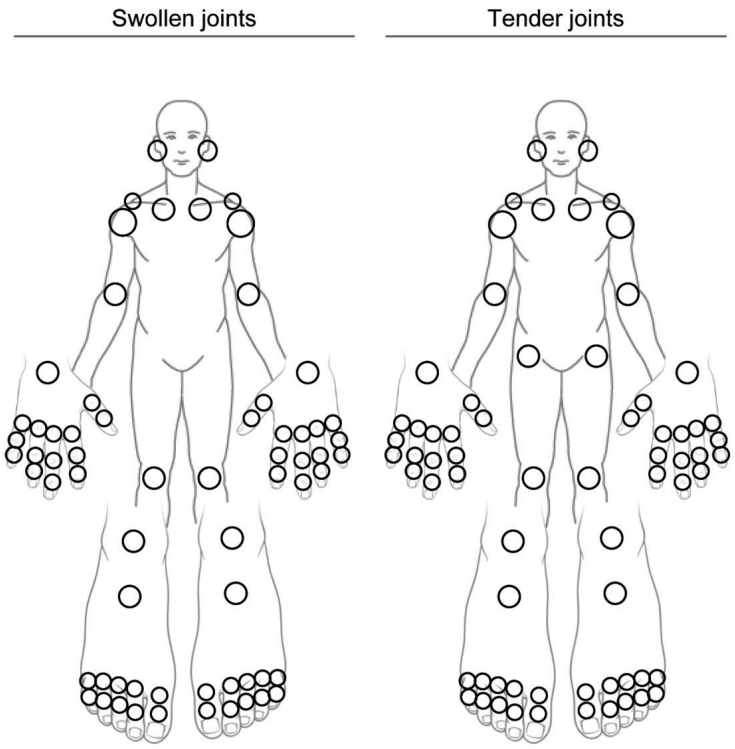
The SJC66/TJC68 is the first instrument fully endorsed within the PsA core outcome measurement set. The 66 swollen and 68 tender joints are assessed (the hips are not assessed for swelling). The joint count is scored as a sum of the tender joints and a sum of the swollen joints (Duarte-García A, et al. 2019).

In this study, SJC66/TJC68 gets measured for all participants.

- SJC66: number of swollen joints
- TJC68: number of tender joints

Figure 8-2 SJC66/TJC68 score

	Swollen joints	Tender joints
Temporomandibular joint	_____(0-2)	_____ (0-2)
Sternoclavicular joints	_____ (0-2)	_____ (0-2)
Acromioclavicular joints	_____ (0-2)	_____ (0-2)
Glenohumeral(s)	_____ (0-2)	_____ (0-2)
Elbow(s)	_____ (0-2)	_____ (0-2)
Wrist(s)	_____ (0-2)	_____ (0-2)
Metacarpal phalangeal joints	_____ (0-10)	_____ (0-10)
Finger Proximal interphalangeal joints	_____ (0-10)	_____ (0-10)
Finger Distal interphalangeal joints	_____ (0-8)	_____ (0-8)
Hip(s)	NA	_____ (0-2)
Knee(s)	_____ (0-2)	_____ (0-2)
Ankle(s)	_____ (0-2)	_____ (0-2)
Tarsus/Midfoot(feet)	_____ (0-2)	_____ (0-2)
Metatarsal phalangeal joints	_____ (0-10)	_____ (0-10)
Toe PIP(s)	_____ (0-10)	_____ (0-10)
Total joint counts	_____ (0-66)	_____ (0-68)



8.5 Efficacy

All efficacy assessments should be recorded in the eCRF. The methods of evaluation and the primary and secondary parameter to be assessed are listed in this section.

8.5.1 Primary endpoint

The primary endpoint of this study is detection rate of PsA. The assessments are measured by the CASPAR including clinical assessment, radiography and blood test. In addition, some values which are included the CASPAR are replaced by the values in Section 8.2.

8.5.1.1 CASPAR

In this study, the CASPAR will be measured for all participants after the EARP questionnaire evaluation and the investigator's judgement are completed in each group. The details of the CASPAR scoring are in the Table 8–2 (Cantini F, et al. 2010).

Table 8–2 CASPAR score

To meet the CASPAR, a patient must have an inflammatory articular disease (inflammatory joint (peripheral) disease, enthesitis, or inflammatory axial disease) with ≥ 3 points from the above criteria.

Criteria	Point
Current PsO	2
Personal history of PsO	1

To meet the CASPAR, a patient must have an inflammatory articular disease (inflammatory joint (peripheral) disease, enthesitis, or inflammatory axial disease) with ≥ 3 points from the above criteria.

Criteria	Point
Family history of PsO	1
Typical PsO nail dystrophy (onycholysis, pitting, hyperkeratosis)	1
Current dactylitis or history of dactylitis	1
Negative rheumatoid factor	1
Hand and foot plain radiography (evidence of juxta-articular new bone formation in hand (including wrist) and feet (including ankle))	1

The items for the CASPAR measurement are as follows.

- Clinical assessment

  Inflammatory joint disease (presence or absence of Inflammatory joint (peripheral) disease, enthesitis and inflammatory axial disease), date of diagnosis for PsO[#], family history of PsO[#], presence or absence of typical psoriatic nail dystrophy (onycholysis, pitting, hyperkeratosis), presence or absence of dactylitis, history of dactylitis

- Blood test

  Rheumatoid factor

- Radiography

  Hand and foot plain X-ray (evidence of juxta-articular new bone formation in hand (including wrist) and feet (including ankle))

Note) #: These values which are included the CASPAR are replaced by the values in Section 8.2.2.2.

8.5.2 Secondary endpoint

The secondary endpoints of this study are as follows.

- Sensitivity, specificity, PPV and NPV
- Description of demographic characteristics, medications and PsO related characteristics

Sensitivity, specificity, PPV and NPV will use CASPAR to determine PsA diagnosis, and be compared between EARP questionnaire (EARP group) and the investigator's judgement (Routine practice group) (Section 8.5.1.1).

Description of demographic characteristics, medications and PsO related characteristics will be compared between PsA and non-PsA patients. Details of the variables are in Section 8.5.2.1 to 8.5.2.3 and the assessment will be measured by the values in Section 8.2 and 8.4.

8.5.2.1 Demographic characteristics

- Age
- Sex
- BMI

- Alcohol consumption status
- Smoking status

8.5.2.2 Medications

- Drug name

8.5.2.3 PsO related characteristics

PsO related medical history

- Duration of PsO
- Family history of PsO
- Family history of PsA
- PASI score
- Presence or absence of hard-to-treat area involvement (scalp, palmoplantar, nails)
- Presence or absence of musculoskeletal symptoms
- Presence or absence of PsO related treatment other than medications

Co-morbidities

- Presence or absence of co-morbidities (heart diseases, stroke, diabetes, hyperlipidemia, hypertension, fatty liver)

NAPSI

- Total Score

SJC66/TJC68

- SJC66: number of swollen joints
- TJC68: number of tender joints

8.6 Safety

Safety assessment is not applicable as no drug is involved.

8.7 Additional assessments

No additional tests will be performed on participants entered into this study.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

Not applicable

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data occurs when a participant:

- Explicitly requests to stop the use of their data (opposition to use participant's data)

and

- No longer wishes to participate in this study

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study must be discontinued and no further assessments conducted.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation. No new Personal Data will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

The study will be considered completed when the last participant enrolled in the study visits and performs the last assessment. Participation in this study has no impact on the type of medical care that the participant will receive during study as well as post-study participation.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

This study is completed after one visit for each participant, and there is no effect on the safety or welfare of the participants due to the study ending after single visit. The investigator or sponsor depending on local regulation will be responsible for informing IRBs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

Not applicable

10.2 Additional Safety Monitoring

Not applicable

10.3 Committees

Not applicable

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

The medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure

that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

All analyses will be performed by a designated CRO.

Descriptive statistics will include n, mean, standard deviation, median, minimum, and maximum for continuous variables and the number and percentage of patients for categorical variables. If necessary, more detailed information will be provided. Statistical comparisons between two groups for continuous variables will be made using independent t-test or Wilcoxon rank sum test, and that for categorical variables using Chi-square test or Fisher’s exact test. All the statistical tests will use a two-sided test at the significance level of 0.05.

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

Further technical details will be specified in the Statistical Analysis Plan, which will be finalized prior to database lock.

12.1 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 all patients as randomized who had assessment for the primary endpoint.
- The PPS will consist of all patients in the FAS who completed the study without major protocol deviations.

12.2 Participant demographics and other baseline characteristics

Analysis on demographic characteristics and PsO related characteristics will be conducted on the FAS and presented by interventional group and overall.

- Demographic characteristics include age, sex, height (cm), weight (kg), BMI, alcohol consumption status and smoking status.
- PsO related characteristics include duration of PsO, family history of PsO, family history of PsA, PASI score, status of hard-to-treat area involvement (scalp, palmoplantar and nails), status of musculoskeletal symptoms, NAPSI (left hand, right hand, left foot, right foot and total), SJC66, TJC68, status of co-morbidities (heart diseases, stroke, diabetes, hyperlipidemia, hypertension and fatty liver), and status of PsO related treatment other than medications.

Continuous variables will be summarized with the number of patients, mean, standard deviation, median, minimum, and maximum and categorical variables will be summarized with the number and percentage of patients. Statistical comparisons between two groups for continuous variables will be made using independent t-test or Wilcoxon rank sum test and that for categorical variables using Chi-square test or Fisher's exact test.

In addition, the number and percentage of patients having at least one prior and ongoing PsO related treatment other than medications will be tabulated by system organ class and preferred term of the MedDRA dictionary. The number and percentage of patients having at least one prior and ongoing medication will be tabulated by therapeutic main group and preferred term of the WHO drug dictionary.

12.3 Treatments

Not applicable

12.4 Analysis supporting primary objectives

The main objective of this study is to compare the detection rate of PsA amongst moderate to severe PsO patients between the EARP group and the Routine practice groups.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is the detection rate of PsA defined as the percentage of patients with true positive results divided by all patients in each EARP and Routine practice group. The true positive results are defined as patients with CASPAR score ≥ 3 among EARP ≥ 3 for the EARP group and among those suspected of PsA by investigator's judgement for the Routine Practice group.

12.4.2 Statistical model, hypothesis, and method of analysis

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 percentage of patients with PsA in each EARP group and Routine practice group, respectively.

The number and percentage of patients with PsA will be presented by each group using the FAS. The point-estimate for the difference of proportion between 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. Superiority will be claimed if the lower limit of the CI is greater than 0.

The primary analysis will be repeated for the PPS using the same model as the one used for the primary analysis.

12.4.3 Sensitivity analyses

Not applicable

12.4.4 Supplementary analysis

Not applicable

12.5 Analysis supporting secondary objectives

12.5.1 Sensitivity, specificity, PPV and NPV

Analysis on sensitivity, specificity, PPV and NPV will be performed on the FAS and PPS and presented by EARP group and Routine practice group.

Sensitivity will be summarized with the number and percentage of patients who have true positive (TP) among those who have true positive (TP) and false negative (FN).

Specificity will be summarized with the number and percentage of patients who have true negative (TN) among those who have true negative (TN) and false positive (FP).

Positive predictive value (PPV) will be summarized with the number and percentage of patients who have true positive (TP) among those who have true positive (TP) and false positive (FP).

Negative predictive value (NPV) will be summarized with the number and percentage of patients who have true negative (TN) among those who have true negative (TN) and false negative (FN).

The statistical significance for the differences between two groups is tested using Chi-square test or Fisher's exact test.

12.5.2 Demographic characteristics and PsO related characteristics

Analysis on the demographic characteristics and PsO related characteristics will be performed on the FAS and PPS and presented by patients with and without PsA.

The following demographic characteristics and PsO related characteristics will be included.

- Demographic characteristics include age, sex, BMI, alcohol consumption status and smoking status.
- PsO related characteristics include duration of PsO, family history of PsO, family history of PsA, PASI score, status of hard-to-treat area involvement (scalp, palmoplantar and nails), status of musculoskeletal symptoms, NAPSI (total), SJC66, TJC68, status of co-morbidities (heart diseases, stroke, diabetes, hyperlipidemia, hypertension and fatty liver), and status of PsO related treatment other than medications.

Continuous variables will be summarized with the number of patients, mean, standard deviation, median, minimum, and maximum and categorical variables will be summarized with the number and percentage of patients. The statistical significance for the differences between two groups is tested using independent t-test or Wilcoxon rank sum test for continuous data and using Chi-square test or Fisher's exact test for the categorical data.

In addition, the number and percentage of patients having at least one prior and ongoing PsO related treatment other than medications will be tabulated by system organ class and preferred term of the MedDRA dictionary. The number and percentage of patients having at least one prior and ongoing medication will be tabulated by therapeutic main group and preferred term of the WHO drug dictionary.

12.6 Interim analyses

No interim analysis will be performed.

12.7 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 DMARDs to reduce any confounding 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 and between 9% and 13.76% of patients with PsO may have undiagnosed PsA (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 alpha=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 about 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.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB for the trial protocol, written ICF, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs, and regulatory authorities as required.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

13.5 Participant Engagement

Not applicable

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB at the study site should be informed according to local regulations.

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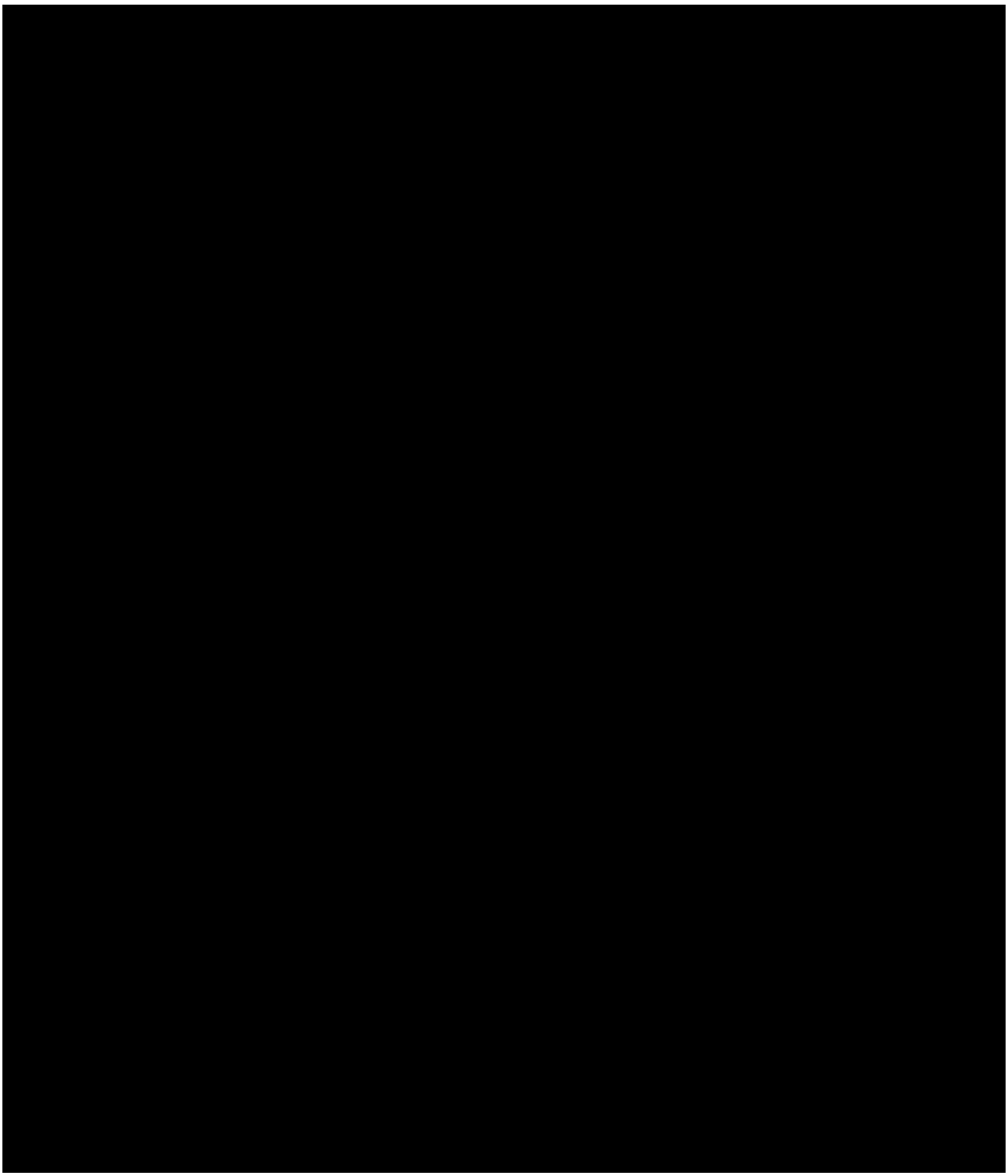
Appendix 1. EARP questionnaire

EARP [redacted]



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