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AIN457/Secukinumab/Cosentyx®

CAIN457FDE04 / NCT04632927

A 28-week, randomized, double-blind, active-controlled, multicenter study to evaluate the efficacy of subcutaneously administered secukinumab compared to ustekinumab in adult patients with psoriatic arthritis and failure of TNFa-inhibitor treatment (AgAIN)

Statistical Analysis Plan (SAP)

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13-Jan-2025	Prior to DB lock	Creation of final version	N/A - First version	NA

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartarte Aminotransferase
BSA	Body Surface Area
[redacted]	[redacted]
CSR	Clinical Study Report
[redacted]	[redacted]
DLQI	Dermatology Life Quality Index
[redacted]	[redacted]
EULAR	European League Against Rheumatism
eCRF	Electronic Case Report Form
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
HAQ-DI©	Health Assessment Questionnaire-Disability Index
[redacted]	[redacted]
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LLT	Low Level Term of MedDRA
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Event
mCPDAI	modified Composite Psoriatic Disease Activity Index
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model for Repeated Measurements
[redacted]	[redacted]
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area Severity Index
[redacted]	[redacted]
PFS	Pre-filled Syringe
PRO	Patient-reported Outcomes
[redacted]	[redacted]
PT	Preferred Term
PsAQoL	Psoriatic Arthritis Quality of Life
RAS	Randomized Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
s.c.	subcutaneously
SD	Standard Deviation

[redacted]	[redacted]
SJC	Swollen Joint Count
SMQ	Standardized MedDRA Query
SOC	System Organ Class
[redacted]	[redacted]
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
TJC	Tender Joint Count
ULN	Upper Limit Normal
VAS	Visual Analog Scale
[redacted]	[redacted]

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe all analyses necessary for the final clinical study report (CSR) for study CAIN457FDE04. The SAP is based on the final study protocol version 01 dated 10-SEP-2024.

Data capture will be performed using an electronic Case Report Form (eCRF). The SAP is based on the latest available version 6.0.

CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specifications (PDS) respectively.

Data will be analyzed by Novartis and/or the designated Contract Research Organization (CRO). Statistical software SAS version 9.4 or higher will be used for generating TFLs.

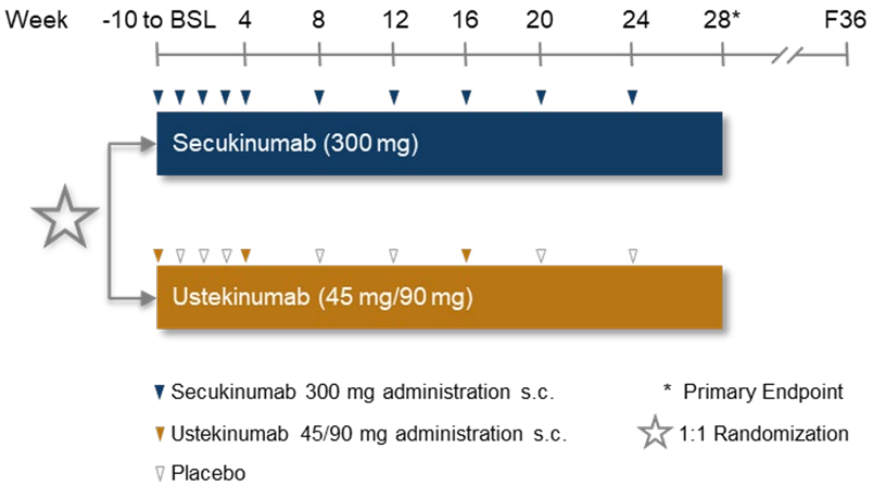
1.1 Study design

This was a 28-week, randomized, double-blind, active-controlled, multicenter study involving 310 adult patients with PsA who failed TNFα inhibitor treatment. The aim of the study was to demonstrate that the efficacy of secukinumab (300 mg s.c.) is superior to ustekinumab (45/90 mg s.c.) in adult patients in terms of achieving an improvement in health assessment questionnaire-disability index (HAQ-DI©) response ≥ 0.35 versus Baseline. Patients were randomized equally to one of the following treatment groups (see Figure 3-1):

- Secukinumab 300 mg s.c. for administration at Week R, 1, 2, 3, 4 followed by dosing every 4 weeks thereafter (i.e. at Week 8, 12, 16, 20 and 24).
- Ustekinumab 45 mg s.c. (or 90 mg s.c. if body weight > 100 kg) for administration at Week R and Week 4 followed by dosing 12 weeks later at Week 16. Placebo to secukinumab were administered at the respective secukinumab dosing time points, i.e. at Week 1, 2, 3, 8, 12, 20 and 24.

The study included a Screening period of up to 10 weeks, a treatment period of 28 weeks with the primary endpoint at Week 28, and a follow-up period of 8 weeks.

Figure 1-1 Study Design



BSL: Baseline, F: Follow-up

At the randomization visit (Baseline) all eligible patients were given an available randomization number that assigned them to one of the two treatment arms. It was ensured that treatment assignment was unbiased and concealed from patients and investigator staff. Subsequently, the investigator entered the randomization number in the eCRF.

A patient randomization list was by or under the responsibility of Novartis Biometrics Department using a validated system ensuring random assignment of treatment groups to randomization numbers in the specified 1:1 ratio (secukinumab group, ustekinumab group). The randomization scheme was reviewed and locked after approval. According to the recommendations given in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guideline "Statistical Principles for Clinical Trials", the used block length was specified in a separate document which was withheld from the study centers. The randomization list was kept sealed in a secure location.

All study sites were provided with a given set of sealed allocation cards.

At the Randomization Visit, the investigator assigned each patient who met all the inclusion criteria and did not fulfill any of the exclusion criteria to the lowest available randomization number, opened the corresponding treatment allocation card and treated the patient with the treatment noted on this card (i.e. secukinumab treatment or ustekinumab treatment).

In order to achieve a balanced weight distribution in each treatment arm, randomization in these 2 arms was stratified by body weight assessed at Day 1 (Baseline visit). The weight was not further controlled in following visits. Stratification ensured a balanced allocation of patients to treatment groups within the 2 weight strata: "body weight ≤ 100 kg" or "body weight > 100 kg". It was expected that approximately 40% of the patients were in the upper weight stratum.

No interim analyses were planned.

As of 31 Jan 2024, all screening/recruitment activities of this study were stopped due to severe recruitment issues, since 36 months after start of screening only 37% (116 of 310 Patients) were recruited although extensive measures to enhance recruitment were taken. Therefore, Amendment 1 was implemented.

In total 119 participants were randomized. Under the previous assumptions for the sample size the power will be ~55%. Hence, only a descriptive analysis will be performed.

1.2 Study objectives, endpoints and estimands

The study objectives and related endpoints are presented in Table 1-1.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• To demonstrate that secukinumab 300 mg s.c. is superior to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement in HAQ-DI© score ≥ 0.35 versus Baseline.	• Proportion of patients achieving a HAQ-DI© response at Week 28.
Secondary objectives	**Endpoints for secondary objectives**
• The efficacy of secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a PASI 90 response.	• Proportion of patients achieving a PASI 90 response at Week 28.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of ≥ 10 mm for the patient's assessment of pain on VAS.	• Proportion of patients achieving an improvement on VAS at Week 28 for patient's assessment of pain.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for the TJC 68.	• Between-treatment difference in change from baseline to Week 28 for the TJC.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher	• Between-treatment difference in change from baseline to Week 28 for the SJC.

compared to ustekinumab 45/90 mg s.c. at Week 28 for the SJC 66.	
• Secukinumab 300 mg s.c. is shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a PASI 100 response.	• Proportion of patients achieving a PASI 100 response at Week 28
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a PASI 75 response.	• Proportion of patients achieving a PASI 75 response at Week 28.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of 10 mm for the patient's global assessment of disease activity (VAS).	• Proportion of patients achieving an improvement on VAS at Week 28 for patient's global disease activity.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of 10 mm for patient's global assessment of psoriasis and arthritis disease activity (VAS).	• Proportion of patients achieving an improvement on VAS at Week 28 for patient's global assessment of psoriasis and arthritis disease activity.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving MDA.	• Proportion of patients achieving MDA at Week 28.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for the LEI.	• Between-treatment difference in change from baseline to Week 28 for the LEI.
• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for the LDI.	• Between-treatment difference in change from baseline to Week 28 for the LDI.

• The mean change from Baseline on secukinumab 300 mg s.c. is higher compared to ustekinumab 45/90 mg s.c. at Week 28 for PsAQoL.	• Between-treatment difference in change from baseline to Week 28 in the PsAQoL.
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving an improvement of ≥ 4 points for FACIT-Fatigue©.	• Proportion of patients achieving a FACIT-Fatigue© response at Week 28. •
• Secukinumab 300 mg s.c. shows a beneficial effect compared to ustekinumab 45/90 mg s.c. at Week 28 based on the proportion of patients achieving a DLQI 0/1 response.	• Proportion of patients achieving a DLQI response of 0/1 at Week 28.
• To evaluate the safety and tolerability of secukinumab 300 mg s.c. compared to ustekinumab 45/90 mg s.c. as assessed by vital signs, clinical laboratory values, and AE monitoring.	• Number and proportion of patients with treatment-emergent AEs as well as descriptive description of vital signs and clinical laboratory values.

[redacted]

AE: adverse event, BSA: body surface area, [redacted] DLQI: Dermatology Life Quality Index, [redacted], EULAR: European League Against Rheumatism, FACIT-Fatigue©: Functional Assessment of Chronic Illness Therapy-fatigue, HAQ-DI©: Health Assessment Questionnaire-Disability Index, [redacted] LDI: Leeds Dactylitis Index, LEI: Leeds Enthesitis Index, [redacted] MDA: Minimal Disease Activity, [redacted] PASI: Psoriasis Area Severity Index, [redacted]

[redacted] PsAQoL: Psoriatic Arthritis Quality of Life, s.c.: subcutaneously, [redacted], SJC: Swollen Joint Count, [redacted] TJC: Tender Joint Count, VAS: Visual Analog Scale, [redacted]

1.2.1 Primary estimand(s)

The primary endpoint variable was the proportion of patients achieving treatment response as defined by a change in HAQ-DI® ≥ 0.35 from baseline to week 28.

The analysis of the primary variable was based on the treatment-policy estimand:

• Analysis set: FAS,

• Variable of interest: proportion of patients achieving treatment response as defined by a change in HAQ-DI© ≥ 0.35 from baseline to week 28,

• Intervention effect: effect between secukinumab 300mg vs. ustekinumab 45mg/90mg regardless of adherence to randomized treatment,

• Summary measure: Odds ratio (OR).

2 Statistical methods

2.1 Data analysis general information

The data was analyzed by Novartis and/or a designated CRO. All analyses will be performed using SAS® statistical software (Version 9.4 or a more recent version), unless otherwise noted.

The analyses was conducted on all patient data after data base lock for the trial. Any data analysis carried out independently by the investigator should have been submitted to Novartis before publication or presentation.

The primary analyses for all efficacy and safety endpoints was carried out after the last patient completed Week 28 assessment.

Aside from analyses mentioned particularly below, all categorical data were summarized as frequencies and percentages and for continuous data, mean, standard deviation (SD), median, minimum, and maximum were presented.

2.1.1 General definitions

The following labels were used for study treatment throughout the analyses:

"Investigational treatment/Secukinumab arm" and "Control treatment/Ustekinumab arm".

The following study drugs were used:

- Investigational treatment/Secukinumab arm

- will receive a dose of secukinumab 300 mg s.c. which consists of 2 injections of the 150 mg pre-filled syringes (PFS) at a frequency shown in Table 2-1..

- Control treatment/Ustekinumab arm
  - Patients weighing ≤ 100 kg at Baseline will receive a dose of 45 mg ustekinumab s.c., which consists of one injection of the 45 mg PFS + one placebo s.c. injection at a frequency shown in Table 2-1 .
  - Patients weighing >100 kg at Baseline will receive a dose of 90 mg ustekinumab s.c., which consists of one injection of the 90 mg PFS + one placebo s.c. injection at a frequency shown in Table 2-1.

Table 2-1 Overview of treatment during the study – type and number of injections

	Screening	Treatment Period										EOS	FUP
Week (relative to randomization)	**-10 to BSL**	**R**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**36**
Visit number	**SV**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Secukinumab 300 mg													
Active injection[1]	-	2	2	2	2	2	2	2	2	2	2	-	-
Ustekinumab[2]													
Patient ≤ 100 kg													
Active injection[2]	-	1	-	-	-	1	-	-	1	-	-	-	-
Placebo injection[3]	-	1	2	2	2	1	2	2	1	2	2	-	-
Patient > 100 kg													
Active injection[2]	-	1	-	-	-	1		-	1	-	-	-	-
Placebo injection[3]	-	1	2	2	2	1	2	2	1	2	2	-	-

BSL = Baseline, EOS = end of study, FUP = follow-up, R = Randomization, SV = Screening Visit, V = Visit

[1] Secukinumab 150 mg PFS: patients randomized to secukinumab will receive 2 active injections;

[2] Ustekinumab dose based on body weight at Baseline: 45 mg for patient ≤ 100 kg (1 active injection); 90 mg for patient > 100 kg (1 active injection)

[3] Secukinumab placebo PFS

"Baseline" was defined as the date, when randomization was performed. Baseline was set to "Day 1". Study Day 1 is defined as the first day of administration of randomized study treatment. Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. visit, lab samples, AEs). For events prior to study drug start date (e.g. time since diagnosis), study day will be negative and calculated as (event date – study drug start date).

Negative study days were applied to events during the screening period.

The study was separated into three periods starting with a "Screening period" (up to 10 weeks prior to randomization), a "treatment period" (starting at randomization up to 28 weeks) and a "follow-up period" of 8 weeks.

Baseline value refers to the value of the last non-missing measurement collected prior to administration of the first dose of study treatment (screening or Baseline visit). A post-Baseline value refers to a measurement taken after the first dose of study treatment.

The difference of measure between post-Baseline and Baseline is called change from Baseline. The percent change from Baseline will be calculated as below:

((post-Baseline value – Baseline value) /Baseline value)*100.

The "on-treatment period" used for safety analyses lasted from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment or end of treatment phase, whichever is later.

"Date of first administration of study treatment" was the date of the earliest documented administration of study drug. This usually should have coincided with the baseline date.

"Date of last administration of study treatment" was defined as the date of the latest documented administration of study drug. This usually should have been either the date documented as date of administration at visit "Week 24" or the date of last administration documented at" the discontinuation visit.

"Last contact" was defined as the last documented date for a patient either within visits or unscheduled data sets (AE, Prior / Concomitant medications, Surgical and Medical Procedures) date patient's assessment documented on patient questionnaires.

2.2 Analysis sets

The Randomized Analysis Set (RAS) consisted of all randomized patients. Unless otherwise specified, miss-randomized patients were to be excluded from the RAS. Misrandomized patients are defined as cases where subjects were mistakenly randomized by the investigator/qualified site staff either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind treatment was not administered to the subject.

The Full Analysis Set (FAS) comprised all patients to whom study treatment (investigational or control treatment) has been assigned by randomization. According to the intent to treat principle, patients were analyzed according to the treatment and strata they had been assigned to during the randomization procedure.

The Safety Set included all patients who received at least one dose of study treatment (investigational or control treatment). Patients were analyzed according to the study treatment received, where treatment received was defined as the first dose of study treatment.

2.2.1 Subgroup of interest

The following subgroups were analyzed as supportive analyses to analyze possible subgroup-by-treatment interaction effects:

- Age (≤ 65 vs. > 65)
- Gender (male vs. female)

- Number of previous TNFα treatment regimens (≤ 2 vs. > 2)

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The following information was presented with regard to patient disposition:

- Number of patients screened
- Number of screening failures
- Reasons for screening failure
- Number of patients randomized
- Number of study completers
- Number of patients who discontinued the study prematurely
- Reasons for premature withdrawal
- Number of treatment completer
- Number of patients who discontinued treatment prematurely
- Reasons for treatment discontinuation
- Protocol deviations
- Number of patients in RAS, FAS and Safety set
- Reason for exclusion from analysis sets.

2.3.2 Protocol deviation

The number and percentage of subjects with protocol deviations will be tabulated by category and deviation for the FAS. Separate summary for protocol deviation due to COVID - 19 will be provided for FAS. Subjects with protocol deviations will be listed with date and study day of occurrence, deviation and severity codes.

The number of subjects included in each analysis set will be tabulated for FAS Reasons for exclusion from analysis sets will be tabulated for the FAS. Patient exclusion from analysis sets will be listed for all subjects with reasons for exclusion (i.e., both protocol and non-protocol deviations).

2.3.3 Demographics and other baseline characteristics

Demographic and other Baseline data including disease characteristics were listed and summarized descriptively by treatment group for the FAS and Safety set.

Categorical data were presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum were presented.

2.3.4 Relevant medical history/ current medical condition

Medical history/ current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will be summarized for the FAS by primary system organ class (SOC), preferred term (PT), treatment group and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The Safety set was used for the analyses of study treatment. Categorical data were summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum were presented.

The duration of exposure to study treatment by treatment group was summarized by means of descriptive statistics using the safety set. In addition, the number of patients with an exposure of at least 4 weeks, of at least 16 weeks, at least 20 weeks and completer (week 24) was displayed. Duration of exposure to the study treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period (expressed as: Duration of exposure = Date of last known dose of study drug – Date of first dose of study drug + 1).

Compliance was calculated based on documented study drug administrations in percent as number of injections performed divided by 10 (= visits with active injections) times 100% and displayed by treatment group. Additionally the percentage of verum injections applied will be calculated as number of visits with active injectionsat baseline, week 4 and week 16 divided by 3 times 100% for patients from the ustekinumab group.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment were listed and summarized according to the ATC classification system, by treatment group for the Safety set. Prior treatments were defined as treatments taken and stopped prior to first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment and the last day of study visit was a concomitant treatment, including those which were started pre-baseline and continued into the treatment period of the study. All prior and concomitant medications will be coded using the latest version of the WHO drug dictionary. Treatments were presented in alphabetical order, by ATC codes and grouped by anatomical main group. Tables also showed the overall number and percentage of patients achieving at least one treatment of a particular ATC.

All summaries will be on the safety set.

2.5 Analysis supporting primary objective(s)

The analyses were conducted on all patient data after data base lock for the trial. The primary analyses for all efficacy and safety endpoints were carried out after the last patient completed Week 28 assessment.

2.5.1 Primary endpoint(s)

The primary aim of the study was to demonstrate that secukinumab 300mg is superior to ustekinumab 45mg/90mg in terms of achieving a HAQ-DI© response ≥ 0.35 in change from baseline to week 28 in adult patients with psoriatic arthritis, who failed previous TNFα inhibitor treatment.

The primary endpoint variable was the proportion of patients achieving treatment response as defined by a change in HAQ-DI© ≥ 0.35 from baseline to week 28.

The analysis of the primary variable was based on the treatment-policy estimand:

- Analysis set: FAS,
- Variable of interest: proportion of patients achieving treatment response as defined by a change in HAQ-DI© ≥ 0.35 from baseline to week 28,
- Intervention effect: effect between secukinumab 300mg vs. ustekinumab 45mg/90mg regardless of adherence to randomized treatment,
- Summary measure: Odds ratio (OR).

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis was that there is no difference in the proportion of subjects fulfilling the HAQ-DI© responder definition at Week 28 between the two treatment arms in the FAS population.

Let p_j denote the proportion of HAQ-DI© responders at Week 28 for treatment group j, j = 0,1, where

- 0 corresponds to the ustekinumab 45mg/90mg treatment arm,
- 1 corresponds to the secukinumab 300mg arm.

No formal tests were performed.

Proportions and 95% confidence intervals were computed for both treatment groups.

The primary endpoint of HAQ-DI© response at Week 28 was analyzed via a multiple logistic regression model with treatment and randomization strata as factors and baseline HAQ-DI© score as a covariate. Odds ratios and confidence intervals were computed for comparisons of secukinumab versus ustekinumab regimen utilizing the logistic model fitted to the data. Results were interpreted exclusively descriptively.

2.5.3 Handling of intercurrent events

Missing data for HAQ-DI© response for data up to Week 28 was replaced as non-response in the sense of worst case analysis. The originally planned replacement using Multiple Imputation (MI) was omitted for all endpoints.

Patients who were unblinded prior to the scheduled time point were considered non-responders from the time of unblinding up to Week 28.

2.5.4 Handling of missing values not related to intercurrent event

Missing values not related to intercurrent events were handled similarly to handling of missing related to intercurrent events.

2.5.5 Sensitivity analyses

Since worst case imputation (assessment as non-response) was used as imputation for missing values for the primary endpoint, sensitivity analysis originally planned with LOCF or worst case imputation was omitted.Subgroup analyses were conducted as supportive analyses to investigate possible subgroup-by-treatment interaction effects for the following subgroups:

- Age ($\leq$ 65 vs. > 65)
- Sex (male vs. female)
- Number of previous TNFα treatment regimens ($\leq$ 2 vs. > 2).

2.5.6 Supplementary analyses

No further supplementary analyses were planned.

2.6 Analysis supporting secondary objectives

The analyses of secondary endpoints were performed using the FAS once all patients had completed the Week 28 assessment. For evaluation of secondary efficacy outcomes, no formal statistical testing procedure was applied.

Some observed parameters were used in this study both as secondary objective and as explorative endpoint. In the SAP the parameters were defined in both sections as appropriate. In the tables, figures and listings (TFL) shells file tables were presented by parameter irrespective of this separation.

2.6.1 Secondary endpoint(s)

Secondary objectives and the corresponding secondary endpoints were presented in chapter 1.2.

2.6.2 Statistical hypothesis, model, and method of analysis

Binary secondary efficacy endpoints like the proportion of patients with a PASI 90 response or Minimal Disease Activity at Week 28 were evaluated presenting rates and 95% confidence intervals. For continuous endpoint variables like the patient's assessment of pain (VAS) or

tender and swollen joint count, course and difference to baseline were presented using sample statistics.

2.6.3 Handling of intercurrent events

Missing data for binary secondary efficacy endpoints (e.g. response of PASI 90, PASI 100, PsAQoL etc.) for data up to Week 28 were handled by worst case imputation (i.e. non-response).

[redacted]

Patients who were unblinded prior to the scheduled time point were considered non-responders from the time of unblinding up to Week 28.

2.6.4 Handling of missing values not related to intercurrent event

No tests will be performed.

2.6.5 Sensitivity analyses

No additional sensitivity analyses were planned for secondary objectives.

2.6.6 Supplementary analyses

No additional supplementary analyses were planned for secondary objectives.

2.7 Safety analyses

Safety measurements include duration of exposure, vital signs, laboratory data and adverse events. All safety endpoints will be summarized using the Safety Set. Patients will be analyzed according to treatment received.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of Baseline data which was summarized where appropriate (e.g. change from Baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths was provided. In particular, summary tables for AEs summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasted from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

2.7.1 Adverse events (AEs)

All information obtained on AEs were displayed by treatment group and patient.

The number (and percentage) of patients with treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) were summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries were provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation.

Adverse events were summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having any AE in each primary system organ class and having each individual AE (PT). Summaries were also presented for AEs by severity and for study treatment related AEs. If a patient reported more than one AE with the same PT; the AE with the greatest severity was presented. If a patient reported more than one AE within the same primary system organ class, the patient was counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events were be summarized.

For the legal requirements of ClinicalTrials.gov and EudraCT, 2 required tables on treatment emergent AEs which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class and PT on the safety set population.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same system organ class and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by system organ class and PT.

In addition, all the treatment emergent AEs will be listed.

The by-subjects listing will include, SOC/PT/Verbatim term, start date, end date, severity, relationship to study drug, whether or not it is a serious AE, action taken with study drug and outcome. Duration will be calculated as (end date – start date + 1) and for ongoing AE (last visit date – start date + 1).

A summary of action taken with number and percentage of subjects will be presented with dose increased, no dose change, dose reduced, drug interrupted, drug withdrawn, not applicable and unknown.

2.7.1.1 Adverse events of special interest / grouping of AEs

The following AE were defined as adverse events of special interest:

Infections and infestations: all terms belonging to MedDRA SOC “Infections and infestation” (10021881)

Hypersensitivity: all terms belonging to MedDRA Standardized MedDRA Query (SMQ) “Hypersensitivity (SMQ)” (20000214)

Malignant or unspecified tumors: all terms belonging to SMQ “Malignant or unspecified tumours (SMQ)” (20000091)

Major Adverse Cardiovascular Events (MACE): all fatal adverse events, all events belonging to the SMQ “Myocardial infarction (SMQ)” (20000047), “Coronary revascularization” (PT 10049887), “Basal ganglia stroke” (PT 10071043), “Brain stem stroke” (PT 10068644), “Cerebellar stroke” (PT 10079062), “Embolic stroke” (PT 10014498), “Haemorrhagic stroke” (PT 10019016), “Heamorrhagic transformation stroke” (PT 10055677), “Ischaemic stroke” (PT 10061256), “Lacunar stroke” (PT 10076994), “Post procedural stroke” (PT 10066591), “Spinal stroke” (PT 10082031), “Stroke in evolution” (PT 10059613), “Thrombotic stroke” (PT 10043647), “Vertebrobasilar stroke” (PT 10082484), any of the following event if the patient was hospitalized due to this event: “Cardiac failure acute” (PT 10007556), “Acute left ventricular failure” (PT 10063081), “Chronic left ventricular failure” (PT 10063083), “Cardiac failure chronic” (PT 10007558), “Cardiac failure congestive” (PT 10007559), “Cardiac failure” (PT 10007554), “Right ventricular failure” (PT 10039163), “Cardiac failure high output” (PT 10007560)

Hepatitis B reactivation: “Hepatitis B reactivation” (PT 10058827)

Suicidal ideation and behavior: “Suicidal ideation” (PT 10042458), “Suicidal behaviour” (PT 10065604).

If an event belongs to more than one category (e.g. Hepatitis B reactivation belongs to the SOC Infection and infestations) it was presented in each category.

2.7.2 Deaths

Deaths were presented by treatment group, primary system organ class, preferred term and study period (on treatment, post treatment).

All deaths in the clinical database will be listed with the investigator-reported principal cause. Deaths occurring after the first dose of study treatment until 30 days after the date of last treatment will be summarized. In addition, deaths occurring after the first dose of study treatment and before the date of last treatment will be summarized.

2.7.3 Laboratory data

All laboratory data were listed by treatment group, patient, and visit/time and if normal ranges were available for a parameter abnormalities were flagged. Summary statistics were be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification were used to compare Baseline to the worst on-treatment value.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Not applicable.

2.7.4.2 Vital signs

All vital signs data were listed by treatment group, patient, and visit/time. Summary statistics were provided by treatment and visit/time. Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit was performed. These descriptive summaries were presented by vital sign and treatment group. Change from baseline was only summarized for patients with both baseline and post-baseline values.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

[redacted]

[redacted]

2.13 Interim analysis

No interim analyses was planned nor conducted.

3 Sample size calculation

As mentioned above, as of 31 Jan 2024, all screening/recruitment activities of this study were stopped due to severe recruitment issues, since 36 months after start of screening only 37% (116 of 310 Patients) were recruited although extensive measures to enhance recruitment were taken. Therefore, Amendment 1 was implemented.

In total, 119 participants were randomized. Under the previous assumptions for the sample size the power will be ~55%. Hence, only a descriptive analysis will be performed.

The following sample size estimation was originally performed for the study: Calculation of the sample size was based on the primary efficacy response, HAQ-DI© at Week 28, for a comparison of secukinumab 300 mg vs. ustekinumab 45 mg / 90 mg in TNFα-IR PsA patients utilizing the FAS. Available data from the FUTURE5 trial within the TNFα-IR subpopulation showed a HAQ-DI© response of secukinumab 300 mg of 57.6% and 56.1% at Weeks 28 and 32, respectively (Non-Responder Imputation). Conservatively, assuming a HAQ-DI© response of at least 57% at Week 28 seems therefore justifiable for secukinumab 300 mg.

Following results from the PSUMMIT2 trial of ustekinumab 45 mg / 90 mg, the proportion of HAQ-DI© responders at Week 24 was 36.1%.

With a HAQ-DI© response of 57% in the secukinumab 300 mg arm and a 36.1% response in the ustekinumab 45 mg / 90 mg arm at Week 28 (corresponding to an odds ratio of 2.35), 140 patients per treatment arm were required to achieve a power of > 90% in order to demonstrate superiority at a significance level of 0.05 using the two group continuity corrected χ^2-test of equal proportions. In order to account for some uncertainties in the underlying assumptions and to compensate for some expected drop-out, a total of 310 patients (155 in the secukinumab 300 mg and 155 in the ustekinumab 45 mg / 90 mg arm) should have been randomized into the study.

Furthermore, this number of patients allowed a power of around 90% in order to claim a significant benefit of secukinumab 300 mg vs. ustekinumab 45 mg / 90 mg in TNFα-IR PsA patients, using the PASI 90 responder definition. Available data from the FUTURE5 trial within the TNFα-IR subpopulation showed a PASI 90 response of secukinumab 300 mg of 62.9% and 57.1% at Weeks 24 and 32, respectively (Non-Responder Imputation). Conservatively, assuming a PASI 90 response of at least 57.1% at Week 28 seemed therefore justifiable for secukinumab 300 mg. Following results from the PSUMMIT2 trial of ustekinumab 45 mg / 90 mg, the proportion of PASI 90 responders at Week 24 was 37.3% and remained stable over time.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

Details on data imputation were already presented in the above sections. No additional information was needed.

5.1.1 Study drug

The eCRF was implemented in a way, that start date and end date of study drug had to be complete. Thus no implementation rule was necessary.

5.1.2 AE date imputation

In case an AE belonged unambiguously to one study period, missing start date parts were imputed in such a way, that the minimal possible start date resulted. In case an AE could be assigned to different study periods including on-treatment depending on the imputation of the missing start date parts (e.g. minimal possible date < date of randomization and maximal possible date > end of study treatment + 30 days, or minimal start date ≤ end of study treatment + 30 days and maximal start date > end of study treatment + 30 days) missing start date parts were imputed such that the earliest on-treatment date resulted.

For missing end date parts date was imputed as maximal possible date.

If this imputation resulted in a end date prior to start date, end date was imputed as start date plus 1 day.

5.1.3 Concomitant medication date imputation

In case a therapy could unambiguously be assigned as concomitant to study drug missing date parts were imputed in such a way, that the minimal possible start date resulted. In case a therapy could be assigned to different study treatment phases depending on the imputation of the missing start date parts (e.g. minimal possible start date < date of randomization and maximal possible start date ≥ date of randomization or minimal end date ≤ date if randomization and maximal end date ≥ date of randomization missing start date parts were imputed such that the maximal possible start date resulted and missing end date parts were imputed such that the minimal possible end date resulted.

If this imputation resulted in a end date prior to start date, then either start date was imputed as end date – 1 or end date was imputed as start date plus 1 day, but such that the therapy was assessed as concomitant medication.

5.1.3.1 Prior therapies date imputation

In case a therapy could unambiguously be assigned as prior to study drug missing date parts were imputed in such a way, that the minimal possible start date resulted and the maximal end date resulted.

5.1.3.2 Post therapies date imputation

In case a therapy could unambiguously be assigned as post study drug missing date parts were imputed in such a way, that the minimal possible start date resulted and the maximal end date resulted.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

AE were coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Severity of AE was assessed by the physician and documented in the electronic case report form (eCRF). No additional grading was performed.

5.3 Laboratory parameters derivations

Laboratory parameters were analyed using the grading from the central lab (high, normal and low).

Additionally the percentage of the following liver triggers or liver events in total and by definition were presented:

	Definition / threshold
Liver trigger	3 x Upper limit normal (ULN) < ALT / AST ≤ 5 x ULN
	1.5 x ULN < Total bilirubin (TBL) ≤ 2 x ULN
Liver events	ALT or AST > 5 x ULN
	ALP > 2 x ULN (in the absence of known bone pathology [HLGT 10005959])
	TBL > 2 x ULN (in the absence of known Gilbert syndrome [Low Level Term (LLT) code = 10018267])
	Potential Hy's Law cases (defined as ALT or AST > 3 x ULN and TBL > 2 x ULN without notable increase in ALP to > 2 x ULN
	Any clinical event of jaundice (or equivalent term [HLT 10008636])

	ALT or AST > 3 x ULN accompanied by (general) malaise (LLT code: 10018066, 10025482, 10025483), fatigue (PT code: 10016256), abdominal pain (PT code: 10000081, 10000084, 10000087), nausea (PT code 10028813), or vomiting (PT code: 10047700), or rash with eosinophilia (LLT code 10058919)
	Any AE potentially indicative of a liver toxicity (hepatic failure (PT code: 10000804, 10057573, 10019663, 10056956), fibrosis and cirrhosis (High level term code 10019669), other liver damage related conditions (PT code 10067125), non-infectious hepatitis (SMQ 20000010); benign, malignant and unspecified liver neoplasms (PT 10077922, 10004269, 10019695, 10027761, 10073069, 10073070, 10027457, 10055110, 10061203)

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

The primary analysis was performed using the Statistical Analysis System (SAS) procedure PROC LOGISTIC.

5.4.2 Analysis supporting secondary objective(s)

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.