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Clinical Development

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A randomized, double-blind, multicenter, 24-week study of subcutaneous secukinumab to assess anti-interleukin-17A treatment in plaque psoriasis patients with coexisting non-alcoholic fatty liver disease (pINPOINt)

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransfease
[redacted]	[redacted]
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MRI	Magnetic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
PASI90	Psoriasis Area and Severity Index
PFS	Prefilled Syringe
PRO	Patient Reported Outcome
[redacted]	[redacted]
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe all analyses necessary for the final clinical study report (CSR). The SAP is based on final study protocol version 01 (Amendment 1) dated 05-Jun-2020. As the study was discontinued prematurely, only an abbreviated analysis will be performed.

1.1 Study design

The study was a randomized, placebo-controlled, double-blind, parallel-group, interventional, multicenter study in patients with moderate to severe plaque psoriasis and coexisting NAFLD.

Patients were randomized 2:1 to either receive secukinumab 300 mg s.c (in 2 x 150 mg PFS) or placebo (in 2 x PFS) at Randomization/Baseline, Week 1, Week 2, Week 3, Week 4 and Week 8 (Treatment Period 1). Starting from Week 12, all patients were planned to receive secukinumab 300 mg s.c. up to Week 20 (Treatment Period 2). Patients who were randomized to placebo during Treatment Period 1 were planned to receive secukinumab 300 mg s.c. at Week 12, Week 13, Week 14, Week 15, Week 16 and Week 20. Patients who were randomized to secukinumab during Treatment Period 1 were planned to receive secukinumab 300 mg s.c. at Week 12, Week 16 and Week 20, and placebo at Week 13, Week 14 and Week 15 to maintain the blind.

It was planned to include 90 patients (60 receiving secukinumab and 30 receiving placebo in Treatment Period 1) into the study.

The primary aim of the study was to demonstrate the superiority of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD with respect to PASI90 response at Week 12. Key secondary objective was to evaluate if there is any evidence for a beneficial effect of secukinumab on ALT values at Week 12.

No interim analysis was planned.

1.2 Study objectives, endpoints and estimands

The following tables shows the objectives and endpoints as specified in the study protocol.

Table 1 Objectives and related endpoints

Objectives	Endpoints
Primary objectives	**Endpoints for primary objectives**
• To demonstrate superiority of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD with respect to PASI90 response at Week 12.	• Proportion of patients achieving PASI90 response at Week 12.
Secondary objectives	**Endpoints for secondary objectives**

Objectives	Endpoints
• To evaluate the effect of secukinumab compared to placebo on hepatic inflammation in patients with moderate to severe psoriasis and NAFLD with respect to serum ALT levels at Week 12.	• Serum ALT level at Week 12.
• To evaluate the effect of secukinumab compared to placebo on quality of life in patients with moderate to severe psoriasis and NAFLD with respect to DLQI at Week 12.	• Proportion of patients achieving DLQI 0/1 at Week 12.

[redacted]

ALT = alanine aminotransferase, , DLQI = dermatology life quality index, 2011, , NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, PASI90 = psoriasis area and severity index,

1.2.1 Primary estimand(s)

The analysis of the primary variable was planned to be based on the following estimand:

- Analysis set: FAS
- Variable of interest: PASI 90 response at Week 12
- Intercurrent event: study discontinuation – effect between secukinumab versus placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD irrespective of adherence to treatment. Patients who discontinued the trial prematurely were counted as non-responders.
- Summary measure: Odds ratio (OR).

It was planned to calculate a "while on treatment" estimand as a sensitivity analysis. It was planned to be based on the following estimand:

- Analysis set: FAS
- Variable of interest: PASI 90 response at Week 12
- Intercurrent event: study discontinuation – effect between secukinumab versus placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD. A patient with a missing assessment will be considered as a responder if he/she has met the response criterion already at the time of drop out. Otherwise, he/she will be considered as a non-responder. Summary measure: OR.

1.2.2 Secondary estimand(s)

Not applicable.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by the CRO using the SAS software Version 9.2. As the study was prematurely discontinued due to low recruitment, center effects or stratification factors were not considered.

2.1.1 General definitions

“Secucinumab 300 mg s.c.” and “Placebo” will be used as terms for treatment groups in the rest of document.

“Date of first administration of study drug/treatment” was defined as the date of the administration of study drug/treatment documented at the randomization visit.

“Date of last administration of study drug/treatment” was defined as the last available date documenting an administration of study drug/treatment.

“Last contact” was defined as the last available date that was documented for a patient irrespective of place of documentation / dataset where the date was given.

“Treatment Period 1” was defined as the period starting with the baseline visit and ending with the visit at Week 12.

“Treatment Period 2” was defined as the period starting with the visit at Week 12 and ending with the visit at Week 24.

Data from the end-of-treatment 1 visit was moved to the originally planned visit closest to the time point of the performance of the end-of-treament 1 visit for patients who discontinued treatment prematurely (irrespective of the reason for discontinuation).

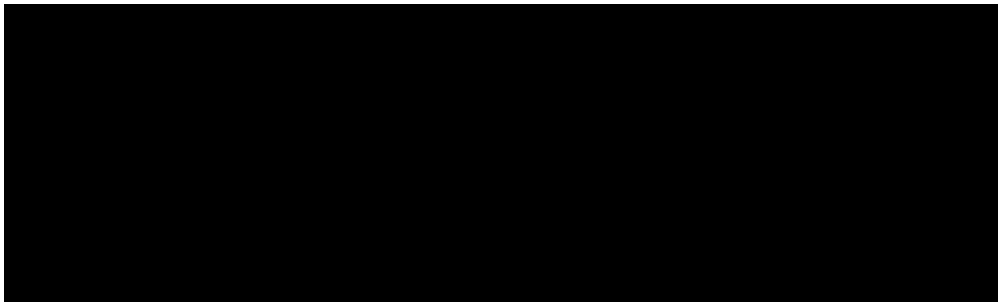
2.2 Analysis sets

The following analysis sets were used in this study:

Randomized Analysis Set (RAS): The RAS was defined as all patients who were randomized. Unless otherwise specified, miss-randomized patients will be excluded from the RAS.

Full Analysis Set (FAS): The FAS comprises all patients to whom study treatment/reference treatment had been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Safety Set: The Safety Set included all patients who received at least one dose of study treatment/reference treatment. Patients were analyzed according to the study treatment received where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.



2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition was described giving the number of patients included, the number of screening failures, number ob patients randomized and the number of patients who completed the study.

2.3.2 Demographics and other baseline characteristics

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

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

Relevant medical histories and current medical conditions at Baseline were summarized by system organ class and preferred term (PT), and by treatment group.

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

2.4.1 Study treatment / compliance

The Safety Set was used for the analyses below. Categorical data was summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 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.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies received prior to and after the start of the study treatment were listed and summarized according to the anatomical therapeutic chemical (ATC) classification system, by treatment group. 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. 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 receiving at least one treatment of a particular ATC.

2.5 Analysis supporting primary objective(s)

2.5.1 Primary endpoint(s)

The primary aim of this study was to demonstrate the superiority of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD with respect to PASI90 response at Week 12.

The primary endpoint variable was the PASI90 response at Week 12.

2.5.2 Statistical hypothesis, model, and method of analysis

The null hypothesis to be rejected was that the OR of a PASI90 response for patients with secukinumab vs. patients with placebo were ≥ 1 after 12 weeks.

Let p_j denote the probability of a PASI90 response at 12 weeks for treatment group j, j=0,1 where

- 0 corresponds to placebo
- 1 corresponds to secukinumab 300 mg

The following hypotheses were tested:

H_0: $(p_0 / 1\text{-}p_0)) / (p_1 / 1\text{-}p_1)) \geq 1$ versus H_A: $(p_0 / 1\text{-}p_0)) / (p_1 / 1\text{-}p_1)) < 1$

The primary analysis was planned to be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment group and center as factors and PASI score at Baseline (Day 1) as covariates. It was planned to present the OR and its 95% confidence interval (CI) and p-value. The primary analysis was based on the FAS and was planned to be performed when all patients had completed the Week 12 assessment.

As the number of patients was small when the study was discontinued only change in PASI was presented.

2.5.3 Handling of intercurrent events

For the analysis of the primary endpoint PASI90 response at Week 12, all patients of the FAS will be included. A patient with a missing assessment was planned to be considered as a non-responder.

2.5.4 Handling of missing values not related to intercurrent event

Not applicable.

2.5.5 Sensitivity analyses

A “while on treatment” estimand was planned to be calculated as a sensitivity analysis. It was planned to be based on the following estimand:

- Analysis set: FAS

- Variable of interest: PASI 90 response at Week 12
- Intercurrent event: study discontinuation – effect between secukinumab versus placebo in patients with moderate to severe chronic plaque-type psoriasis and NAFLD. A patient with a missing assessment was considered as a responder if he/she had met the response criterion already at the time of drop out. Otherwise, he/she was considered as a non-responder.
- Summary measure: OR.

2.5.6 Supplementary analyses

Not applicable.

2.6 Analysis supporting secondary objectives

As the study was discontinued prematurely only the analysis for the key secondary objective (ALT level) and course of DLQI were analyzed.

2.6.1 Secondary endpoint(s)

The analysis of historic data from non-NAFLD patients suggested that the distribution of ALT values might be highly skewed to the left; however, after a log-transformation the distribution appeared quite symmetric, bell-shaped and could be well approximated by a normal distribution. Therefore, the log-transformed ALT-values was planned to be used for the analysis.

For this secondary objective, this study was meant as a Proof-of-Concept study, i.e. to evaluate if there is any evidence for a beneficial effect on this endpoint and to provide the basis for the planning of further, confirmatory studies; therefore a Bayesian methodology seemed adequate for the analyses of possible drug effects on ALT.

DLQI at Week 12

The DLQI measures functional disability of adult patients with dermatological disorders and had been utilized as a relevant clinical measure in a range of dermatology clinical trials. The DLQI is a simple, validated, self-administered 10-item questionnaire. The instrument contains 6 functional scales (i.e. symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment).

Each question is answered with the following response: “not at all,” “a little,” “a lot,” or “very much”. Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired.

2.6.2 Statistical hypothesis, model, and method of analysis

It was planned to produce a sample from the posterior distribution of the difference between treatments of the log(ALT) levels using the BAYES-option in SAS PROC GENMOD (with the default, non-informative prior). These posterior samples were planned to be re-transformed (exponentiated) and the percentage of samples < 1, $< .9$, $<.8$ and $<.7$ (corresponding to the posterior probabilities of any reduction resp. reductions of at least 10%, 20% or 30% of ALT

levels under secukinumab compared to placebo) were planned to be calculated. It was specified that the study will suggest to continue the development of secukinumab for hepatic inflammation, if the posterior probability of any effect (significance) was at least 90% and if the posterior probability of a relevant effect (> 20% reduction) was at least 50%.

It was planned to derive for the total DLQI as well as for each of its 7 sub-dimensions the percentage change from baseline. Descriptive summary statistics should have been provided for absolute values as well as for the percentage change by visit and treatment group. Additionally, the percentage of patients achieving a DLQI-score of 0 or 1 (DLQI 0/1) was planned to be tabulated.

2.6.3 Handling of intercurrent events

Missing values of key secondary endpoints were not replaced. Other outcomes were not analyzed.

2.6.4 Handling of missing values not related to intercurrent event

Missing values of key secondary endpoints were not replaced. Other outcomes were not analyzed.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

For all safety analyses, the Safety Set was used. All listings and tables were presented by treatment group.

Safety summaries (tables, figures) included only data from the on-treatment period with the exception of Baseline data, which were summarized where appropriate (e.g. change from Baseline summaries). In particular, summary tables for AEs summarized only on-treatment events, with a start date during the on-treatment period (i.e. treatment-emergent AEs as defined below).

2.7.1 Adverse events (AEs)

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

The number (and percentage) of patients with treatment-emergent AEs was summarized in the following ways:

- By treatment group, primary SOC and PT.
- By treatment group, primary SOC, PT and maximum severity.

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

[redacted]

2.7.2 Deaths

A summary for deaths including on-treatment and post-treatment deaths was provided.

2.7.3 Laboratory data

All laboratory data were listed by treatment group, patient, and visit and if normal ranges are available abnormalities were flagged.

It was planned to provide summary statistics by treatment and visit and change from baseline.

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, and if ranges were available, abnormalities were flagged.

It was planned to perform analysis of the vital sign measurements using summary statistics for the change from Baseline for each post-Baseline visit by vital sign and treatment group.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

[redacted]

[redacted]

2.12 Other Exploratory analyses

Not applicable.

2.13 Interim analysis

No interim analysis was planned.

[redacted]

[redacted]

4 Change to protocol specified analyses

Due to premature discontinuation of the study after low recruitment, the following changes were made:

- RAS and FAS population were identical, thus a separate analysis of the RAS population was omitted.
- Statistical modeling of the primary endpoint and presentation of percentages of patients reaching PASI90 was omitted. Only the course of PASI was presented.
- No imputation for missing values was performed. All data was analyzed as observed.
- The sensitivity analysis for the primary objective was omitted.
- Bayes analyses of the key secondary objective was omitted. Only sample statistics for ALT were presented. No log-transformation of ALT values was performed.
- DLQI data was only listed by treatment group, patient and visit.
- Summary statistics for laboratory values were omitted.
- Sample statistics for vital signs by visit and change from baseline were omitted.

[redacted]

5 Appendix

Not applicable, as no additional information is necessary.

6 Reference

Langley RG, Elewski BE, Lebwohl M, et al (2014) Secukinumab in plaque psoriasis – results of two phase 3 trials. N Engl J Med; 371: 326-38.