NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharma GmbH

Generic Drug Name

Secukinumab

Trial Indications

Plaque psoriasis
Non-alcoholic fatty liver disease

Protocol Number

CAIN457ADE15

Protocol Title

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)

Clinical Trial Phase

Phase 3b

Phase of Drug Development

Phase IIIb

Study Start/End Dates

Study Start Date: February 2020
Primary Completion Date: June 2021
Study Completion Date: July 2021

Reason for Termination

This study was prematurely discontinued after the enrollment of 10 patients, because the recruitment was too slow to achieve the planned number of patients within a reasonable time frame. No safety issues led to the decision to terminate the study prematurely.

Study Design/Methodology

This study was a randomized, placebo-controlled, doubleblind (investigator and patient), parallel-group, interventional, multicenter study in patients with moderate to severe plaque psoriasis and coexisting NAFLD. The study consisted of 3 periods: Screening period (up to 4 weeks prior to enrollment/randomization): Assessment of patients' eligibility and tapering prohibited medication.

Treatment Period 1 (baseline through Week 12): Eligible patients were randomized at a ratio of 2:1 to either receive secukinumab 300 mg s.c. (in 2 × 150 mg prefilled syringes [PFS]) or placebo (in 2 × PFS) at randomization/baseline and subsequently at Weeks 1, 2, 3, 4, and 8.

Treatment Period 2 (Week 12 through Week 24): Starting from Week 12, all patients received secukinumab 300 mg s.c. up to Week 20. Patients who were randomized to placebo during Treatment Period 1 received secukinumab 300 mg s.c. at Weeks 12, 13, 14, 15, 16, and 20. Patients who were randomized to secukinumab during Treatment Period 1 received secukinumab 300 mg s.c. at Weeks 12, 16, and Week 20, and additionally placebo injections at Weeks 13, 14, Week 15 (in order to maintain the blind until study end).

The planned duration of placebo-controlled treatment was 20 weeks; final study assessments were performed at Week 24 (without further injection). A total of 90 patients were planned to be randomized at a ratio of 2: 1 to either the secukinumab or placebo group. In fact, the sample size was smaller than planned, because recruitment was stopped early.

A total of 47 patients were screened and only 10 patients were randomized (7 to the secukinumab group and 3 to the placebo group) before early termination of the study.

Centers

8 centers in 2 countries: Germany (7), Spain (1)

Objectives:

The primary study objective was to demonstrate superiority of secukinumab compared with placebo in patients with moderate to severe chronic plaque-type psoriasis and non-alcoholic fatty liver disease (NAFLD) with respect to PASI90 response at Week 12.

The secondary study objectives were i) to evaluate the effect of secukinumab compared with placebo on hepatic inflammation in patients with moderate to severe psoriasis and NAFLD with respect to serum alanine aminotransferase (ALT) levels at Week 12, and; ii) to evaluate the effect of secukinumab compared with placebo on quality of life in patients with moderate to severe psoriasis and NAFLD with respect to the Dermatology Life Quality Index (DLQI) score at Week 12.

Test Product, Dose, and Mode of Administration

Secukinumab 2 x 150 mg solution for s.c. injection in pre-filled syringe.

Statistical Methods

The final analysis was performed using the SAS software Version 9.2. The following analysis sets were used:

Randomized Analysis Set (RAS): Defined as all patients who were randomized. Unless otherwise specified, miss-randomized patients were excluded from the RAS.

Full Analysis Set (FAS): Comprised all patients to whom study treatment/reference treatment had been assigned by randomization. According to the ITT principle, patients were analyzed according to the treatment they have been assigned to during the randomization procedure. As RAS and FAS populations were identical no separate analysis of the RAS population was performed.

Safety Set (SAF): 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" was 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.

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

As per study protocol, the primary analysis was planned to be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model. It was planned to present the Odds Ratio and its 95%-confidence interval and p-value. The primary analysis was to be based on the FAS and was planned to be performed when all patients had completed the Week 12 assessment. The planned null hypothesis to be rejected was that the Odds Ratio of a PASI90 response for patients with secukinumab vs. patients with placebo is ≥1 after 12 weeks.

Due to the premature study termination and the limited number of treated patients with available data (7 patients in the secukinumab group and 3 patients in the placebo group), the extent of the originally planned statistical analyses of efficacy data was limited to descriptive summaries (absolute values per visit and changes from baseline; presented as mean, standard deviation, median, and minimum/maximum) for the PASI score, ALT values, and DLQI scores. In addition, PASI score values were listed per patient and visit. Adverse events were coded using the MedDRA terminology and presented using tabulated summaries at the system organ class and preferred term levels showing the absolute and relative frequencies of patients with event. In addition, adverse events were listed by patient. Likewise, laboratory values were listed by patient over time.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male/female patients, 18 years or older

- Moderate to severe plaque-type psoriasis, candidate for systemic therapy

- Diagnosis of NAFLD by either ultrasound at Screening or liver histology within 6 months before Baseline

- BMI > 25 kg/ m 2

- ALT 1.2 to 3.0 × ULN

- MRI confirmed Liver fat ≥ 8% at Screening

Exclusion Criteria:

- Forms of psoriasis other than chronic plaque-type Psoriasis

- Drug induced psoriasis

- Pregnant or nursing (lactating) women

- Women of child bearing potential unless they are using effective methods of contraception

- Ongoing use of prohibited treatments

- Previous treatment with biological drug targeting IL-17 or the IL-17 receptor

- Past medical history record of infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to Screening

- Unstable weight over the last 6 months prior to Screening.

- Type I diabetes, or uncontrolled diabetes (Type I or Type II) defined as HbAlc ≥ 10% at screening.

- Evidence of hepatic decompensation or severe liver impairment or cirrhosis

- History of liver transplantation or planned liver transplant or biliary diversion.

- Presence or history of other liver disease

- Current, or history of, significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening

- Prior or planned bariatric surgery

- Inability or unwillingness to undergo MRI of the abdomen

- Past medical history record of infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to Screening

Participant Flow Table

Overall Study

	Investigational Arm - secukinumab	Control Arm - placebo	Total
Arm/Group Description	secukinumab 300mg s.c. weekly in first 4 weeks, followed by q4w up to Week 20; and placebo 300mg s.c. at weeks 13, 14 and 15 to maintain the blind	placebo 300 mg s.c. weekly in first 4 weeks, followed by q4w up to Week 8; and secukinumab 300 mg s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20	
Started	7	3	10
Completed	3	1	4
Not Completed*	4	2	6
Adverse Event	0	1	1
Study terminated by Sponsor	4	1	5

*Patients who were still in the study when the sponsor terminated the study were counted as 'non-completers'

Baseline Characteristics

	Investigational Arm - secukinumab	Control Arm - placebo	Total
Arm/Group Description	secukinumab 300mg s.c. weekly in first 4 weeks, followed by q4w up to Week 20; and placebo 300mg s.c. at weeks 13, 14 and 15 to maintain the blind	placebo 300 mg s.c. weekly in first 4 weeks, followed by q4w up to Week 8; and secukinumab 300 mg s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20	
Number of Participants [units: participants]	7	3	10
Age Continuous (units: years) Mean ± Standard Deviation			

	41.6±11.8	32.0±16.8	38.7±13.3
Sex: Female, Male (units: Participants) Count of Participants			
Female	4	0	4
Male	3	3	6
Race/Ethnicity, Customized (units: Participants)			
White	7	3	10
Age Categorical (units:Participants) Count of Participants			
<=18 years	0	0	0
Between 18 and 65 years	7	3	10
>=65 years	0	0	0

Primary Outcome Results

Mean and SD Change from baseline of PASI score up to week 12 (Full Analysis Set)

(Time Frame: 12 weeks)

Psoriasis Area and Severity Index (PASI) 90 response is defined as ≥ 90% improvement (reduction) in PASI score compared to Baseline The primary analysis was planned to be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model. It was planned to present the Odds Ratio and its 95%-confidence interval and p-value. The planned null hypothesis to be rejected was that the Odds Ratio of a PASI90 response for patients with secukinumab vs. patients with placebo is ≥1 after 12 weeks. Due to the premature study termination and the limited number of treated patients with available data (7 patients in the secukinumab group and 3 patients in the placebo group), the extent of the originally planned statistical analyses of efficacy data was limited to descriptive summaries (absolute values per visit and changes from baseline; presented as mean and standard deviation) for the PASI score.

	Investigational Arm - secukinumab	Control Arm - placebo
Arm/Group Description	secukinumab 300mg s.c. weekly in first 4 weeks, followed by q4w up to Week 20; and	placebo 300 mg s.c. weekly in first 4 weeks, followed by q4w up to Week 8; and secukinumab 300 mg s.c.

	placebo 300mg s.c. at weeks 13, 14 and 15 to maintain the blind	weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20
Number of Participants Analyzed [units: participants]	7	3
Percentage of participants achieving ≥ 90% improvement (reduction) in PASI score compared to Baseline (units: Mean) Mean ± Standard Deviation		
Baseline (n=4,2)	15.7 ± 4.22	15.9 ± 3.39
Week 12 (n=7,3)	0.8 ± 1.14	13.4 ± 0.35

Secondary Outcome Results

Serum Alanine Aminotransferase (ALT) level

(Time Frame: 12 weeks)

ALT is an enzyme that the liver releases when it becomes inflamed or damaged. ALT level measures liver function Parameter. Normal range of values for ALT is about 7 to 56 units per liter (U/L). Higher levels of ALT in the blood indicate more liver problems. Due to the premature study termination and the limited number of treated patients with available data (7 patients in the secukinumab group and 3 patients in the placebo group), the extent of the originally planned statistical analyses of efficacy data was limited to descriptive summaries (absolute values per visit and changes from baseline; presented as mean and standard deviation) for the ALT score.

	Investigational Arm - secukinumab	**Control Arm - placebo**
Arm/Group Description	secukinumab 300mg s.c. weekly in first 4 weeks, followed by q4w up to Week 20; and placebo 300mg s.c. at weeks 13, 14 and 15 to maintain the blind	placebo 300 mg s.c. weekly in first 4 weeks, followed by q4w up to Week 8; and secukinumab 300 mg s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20
Number of Participants Analyzed [units: participants]	7	3
Serum Alanine Aminotransferase (ALT) level (units: U/L) Mean ± Standard Deviation		

Baseline (n=4,2)	60.5 ± 35.73	89.0 ± 15.56
Week 12 (n=7,3)	43.3 ± 12.76	85.5 ± 20.51

Mean and SD of DLQI at week 12

(Time Frame: 12 weeks)

Dermatology Life Quality Index (DLQI) is calculated by summing the score of each domain resulting in a maximum of 30 and a minimum of 0. The higher the score, the more Quality of Life was impaired. Meaning of DLQI Scores: 0-1 = no effect at all on patient's life, 2-5 = small effect on patient's life, 6-10 = moderate effect on patient's life, 11-20= very large effect on patient's life, 21-30 = extremely large effect on patient's life. Due to the premature study termination and the limited number of treated patients with available data (7 patients in the secukinumab group and 3 patients in the placebo group), the extent of the originally planned statistical analyses of efficacy data was limited to descriptive summaries (absolute values per visit and changes from baseline; presented as mean and standard deviation) for DLQI scores.

	Investigational Arm - secukinumab	**Control Arm - placebo**
Arm/Group Description	secukinumab 300mg s.c. weekly in first 4 weeks, followed by q4w up to Week 20; and placebo 300mg s.c. at weeks 13, 14 and 15 to maintain the blind	placebo 300 mg s.c. weekly in first 4 weeks, followed by q4w up to Week 8; and secukinumab 300 mg s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20
Number of Participants Analyzed [units: participants]	7	3
Mean and SD of DLQI at week 12 (units: Mean) Mean ± Standard Deviation		
Baseline (n=7,3)	11.3 ± 5.56	8.0 ± 8.49
Week 12 (n=7,3)	0.3 ± 0.50	7.0 ± 8.49

Safety Results

All-Cause Mortality

	Investigational Arm - secukinumab N = 7	Control Arm - placebo N = 3
Arm/Group Description	secukinumab 300mg s.c. weekly in first 4 weeks, followed by q4w up to Week 20; and placebo 300mg s.c. at weeks 13, 14 and 15 to maintain the blind	placebo 300 mg s.c. weekly in first 4 weeks, followed by q4w up to Week 8; and secukinumab 300 mg s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20
Total participants affected	0 (0.00%)	0 (0.00%)

Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) and Serious Adverse Events were collected after signature of the informed consent and then up to 24 weeks
Additional Description	AEs and SAEs are any untoward sign or symptom that occurs during the study treatment
Source Vocabulary for Table Default	24.1
Assessment Type for Table Default	Systematic Assessment

Adverse Events	**Investigational Arm - secukinumab** secukinumab 300mg s.c. weekly in first 4 weeks, followed by q4w up to Week 20; and placebo 300mg s.c. at weeks 13, 14 and 15 to maintain the blind	**Control Arm - placebo** placebo 300 mg s.c. weekly in first 4 weeks, followed by q4w up to Week 8; and secukinumab 300 mg s.c. weekly for 4 weeks starting at Week 12, followed by q4w up to Week 20
Total # Affected by any Serious Adverse Event	1	0
Total # at Risk of any Serious Adverse	7	3

Event		

Summary of adverse events (SAF)

	Secukinumab N=7 n (%)	Placebo N=3 n (%)	Total N=10 n (%)
Patients with			
Any AEs	5 (71.4)	2 (66.7)	7 (70.0)
Non-serious AE	4 (57.1)	2 (66.7)	6 (60.0)
Serious AEs	1 (14.3)	0	1 (10.0)
Fatal AEs/death	0	0	0
AEs leading to discontinuation of study drug treatment	0	1 (33.3)	1 (10.0)
Requiring additional treatment	1 (14.3)	2 (66.7)	3 (30.0)
Any AE preferred term			
Blood CPK increased	1 (14.3)	1 (33.3)	2 (20.0)
Nasopharyngitis	2 (28.6)	0	2 (20.0)
Headache	1 (14.3)	1 (33.3) [a]	2 (20.0)
Abdominal pain upper	1 (14.3)	0	1 (10.0)
ALT increased	0	1 (33.3) [a]	1 (10.0)
AST increased	1 (14.3)	0	1 (10.0)
Back pain	1 (14.3)	0	1 (10.0)
Cholelithiasis	1 (14.3)	0	1 (10.0)
Dyspepsia	1 (14.3)	0	1 (10.0)
Erythema	1 (14.3)	0	1 (10.0)
Haemorrhoids thrombosed	0	1 (33.3)	1 (10.0)
Hypertension	1 (14.3)	0	1 (10.0)
Hypertriglyceridaemia	0	1 (33.3) [a]	1 (10.0)
Hypothyroidism	1 (14.3)	0	1 (10.0)
LDL increased	1 (14.3)	0	1 (10.0)
Myalgia	0	1 (33.3)	1 (10.0)
Oral herpes	1 (14.3)	0	1 (10.0)
Psoriasis	0	1 (33.3) [b]	1 (10.0)
Urinary sediment abnormal	1 (14.3)	0	1 (10.0)
Urine analysis abnormal	1 (14.3)	0	1 (10.0)

Note: MedDRA version: V24.1. All data provided in the table are based on number of patients.
Patients in the placebo group received their first active injection at Week 12.

a: AE occurred at/after having received an active injection at Week 12.

b: This AE led to premature treatment discontinuation after the 4th injection.

Other Adverse Events by System Organ Class

Conclusion:

This study was prematurely terminated after the enrollment of 10 patients, because no sufficient patient recruitment could be achieved within a reasonable time frame. Hence, no reliable conclusions on the efficacy and safety of secukinumab vs. placebo could be drawn in the scope of the study objectives. However, the few efficacy data suggested stronger improvements in PASI and DLQI upon treatment with secukinumab compared with placebo, while no potential safety issues were identified with secukinumab.

Date of Clinical Trial Report

April 12th 2022