NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

secukinumab

Trial Indication(s)

Plaque psoriasis

Protocol Number

CAIN457AUS02

Protocol Title

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effect of secukinumab on aortic vascular inflammation and cardiometabolic biomarkers after 12 weeks of treatment, compared to placebo, and up to 52 weeks of treatment with secukinumab in adult subjects with moderate to severe chronic plaque-type psoriasis

Clinical Trial Phase

Phase 4

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: February 2016 (Actual)
Primary Completion Date: April 2017 (Actual)
Study Completion Date: February 2018 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in 91 patients with moderate to severe plaque psoriasis. The study consisted of four periods: Screening (from 1 to 4 weeks); Double-blind Treatment Period (12 weeks); Double-blind Induction Period (4 weeks); and Open-label Treatment Period (36 weeks).

Centers

United States (12)

Objectives:

Primary objective

The primary objective was to evaluate the effect of secukinumab 300 mg subcutaneous (sc) compared to placebo on aortic vascular inflammation with respect to the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta. The primary analysis time point was at Week 12.

Secondary objectives

- To evaluate the effect of secukinumab compared to placebo with respect to change from baseline in cardiometabolic biomarkers (cardiometabolic function (lipid particle size, HDL function (cholesterol efflux)), measures of inflammation (TNF-Alpha, IL-6, C reactive protein (CRP)), adiposity (leptin and adiponectin), insulin resistance (insulin levels/glucose to yield homeostatic model assessment-insulin resistance (HOMA-IR), and markers predictive of diabetes (apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A)) at Week 12

- To evaluate the effect of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis with respect to change from baseline in the Psoriasis Area and Severity Index (PASI) 75, 90, and 100 response rates at Week 12

- To evaluate the effect of secukinumab compared to placebo in patients with moderate to severe chronic plaque-type psoriasis with respect to the Novartis Investigator's Global Assessment modified 2011 (IGA mod 2011) 0 or 1 response at Week 12

- To evaluate the effects of secukinumab compared to placebo with respect to change from baseline in the Dermatology Life Quality Index (DLQI) total score at Week 12

- To evaluate the clinical safety and tolerability of secukinumab as assessed by vital signs, clinical laboratory variables, and adverse event monitoring

Test Product (s), Dose(s), and Mode(s) of Administration

secukinumab 300 mg (two 150 mg dose subcutaneous injections of secukinumab)

Statistical Methods

The primary efficacy variable was the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the whole aorta obtained via FDG-PET/CT scans. The primary analysis time point was at Week 12. The primary efficacy variable was analyzed by an analysis of covariance (ANCOVA) model with treatment, baseline, and body weight (<90 kg, ≥90 kg) as explanatory variables. The analysis was based on Full Analysis Set.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Males and females at least 18 years of age with moderate to severe plaque psoriasis

Exclusion Criteria:
- Forms of psoriasis other than chronic plaque psoriasis
- Previous exposure to IL-17A or IL-17 receptor targeting agents.
- Other active or ongoing disease that may interfere with evaluation of psoriasis or places the patient at unacceptable risk
- Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Treatment period 1

	Secukinumab	Placebo
Started	46	45
Completed	44	42
Not Completed	2	3
Adverse Event	2	2
Withdrawal by Subject	0	1

Treatment period 2

	Secukinumab	Placebo
Started	44[1]	42
Completed	41[2]	37
Not Completed	3[2]	5

Adverse Event	2	0
Lack of Efficacy	1	0
Lost to Follow-up	0	2
Withdrawal by Subject	0	2
Protocol Violation	0	1

[1] Completed Treatment Period 1 and continued to Treatment Period 2
[2] Completed Treatment Period 2

Baseline Characteristics

	Secukinumab	Placebo	Total
Number of Participants [units: participants]	46	45	91
Age Categorical (units:) Count of Participants (Not Applicable)			
<=18 years	0	0	0
Between 18 and 65 years	41	39	80
>=65 years	5	6	11
Sex: Female, Male (units:) Count of Participants (Not Applicable)			
Female	13	17	30
Male	33	28	61

Race/Ethnicity, Customized
(units: Participants)

Caucasian	36	36	72
Black	1	3	4
Asian	6	2	8
Other	3	4	7

Summary of Efficacy

Primary Outcome Result

Aortic vascular inflammation as measured by FDG-PET/CT

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Aortic vascular inflammation as measured by FDG-PET/CT (units: target to background ratio (TBR)) Mean ± Standard Deviation		
Baseline	1.6615 ± 0.37380	1.6333 ± 0.33228
Change from Baseline at Week 12	0.0143 ± 0.25520	0.0655 ± 0.28086

Statistical Analysis

Groups	Secukinumab, Placebo	Statistical analysis (Analysis of Covariance) of change from baseline in

		target to background ratio for regions of the aorta at Week 12 (Full Analysis Set)
Superiority Test		This superiority trial compares secukinumab with placebo with a view of demonstrating the superiority of secukinumab over placebo with regards to a specific outcome measure.
P Value	0.3712	
Method	ANCOVA	
Other Least Square Mean	-0.053	
Standard Error of the mean	0.059	
95 % Confidence Interval 2-Sided	-0.169 to 0.064	

Secondary Outcome Results

Change in Adiponectin total

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in Adiponectin total (units: ng/mL) Mean ± Standard Deviation		

Baseline	18799.0 ± 18608.48	19475.00 ± 18343.00
Change from Baseline at Week 12	1594.90 ± 15146.84	-1076.40 ± 14565.60

Change in Apolipoprotein B

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in Apolipoprotein B (units: ng/mL) Mean ± Standard Deviation		
Baseline	0.1014 ± 0.04651	0.1033 ± 0.04451
Change from Baseline at Week 12	0.0020 ± 0.06331	0.0017 ± 0.04835

Change in CRP

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in CRP (units: mg/L) Mean ± Standard Deviation		
Baseline	6.1525 ± 8.23016	7.8676 ± 7.59860
Change from Baseline at Week 12	-1.0016 ± 9.45281	1.1622 ± 15.84088

Change in Cholesterol

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in Cholesterol (units: mg/dL) Mean ± Standard Deviation		
Baseline	179.350 ± 30.01243	178.707 ± 38.92573
Change from Baseline at Week 12	10.6000 ± 30.27379	-8.4878 ± 35.18247

Change in Fetuin A

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in Fetuin A (units: ng/mL) Mean ± Standard Deviation		
Baseline	988677.800781 ± 488494.3491043	1169947.724848 ± 79644.6884632
Change from Baseline at Week 12	90810.212003 ± 444791.4700461	45731.298018 ± 452743.5932412

Change in Ferritin

	Secukinumab	Placebo
Number of Participants Analyzed [units:	46	45

participants]		
Change in Ferritin (units: ng/mL) Mean ± Standard Deviation		
Baseline	111.953 ± 91.17931	122.040 ± 114.8715
Change from Baseline at Week 12	-6.1006 ± 60.71995	-17.118 ± 63.86703

Change in GlycA

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in GlycA (units: µmol/L) Mean ± Standard Deviation		
Baseline	413.860 ± 65.34929	439.622 ± 60.44873
Change from Baseline at Week 12	0.5152 ± 59.46394	-1.5420 ± 40.25958

Change in HDL Cholesterol

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in HDL Cholesterol (units: mg/dL) Mean ± Standard Deviation		
Baseline	43.3000 ±	43.0732 ±

	10.20357	12.52276
Change from Baseline at Week 12	-0.7500 ± 8.80195	-1.1220 ± 8.10924

Change in HDL function (cholesterol efflux)

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in HDL function (cholesterol efflux) (units: ratio of the pleated serum to removal of cholesterol) Mean ± Standard Deviation		
Baseline	0.9535 ± 0.18986	1.0456 ± 0.17819
Change from Baseline at Week 12	0.1473 ± 0.23262	0.0541 ± 0.21902

HDL Particle Total

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
HDL Particle Total (units: µmol/L) Mean ± Standard Deviation		
Baseline	29.2875 ± 5.38184	29.3634 ± 6.27442
Change from Baseline at Week 12	-0.1375 ± 5.22900	-0.1707 ± 5.12973

HDL size

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
HDL size (units: nm) Mean ± Standard Deviation		
Baseline	8.9350 ± 0.53280	8.9585 ± 0.56656
Change from Baseline at Week 12	0.0500 ± 0.47932	0.0073 ± 0.34161

HOMA-IR

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
HOMA-IR (units: units) Mean ± Standard Deviation		
Baseline	3.4901 ± 3.02479	5.5112 ± 6.22334
Change from Baseline at Week 12	0.9563 ± 2.23669	-1.2764 ± 5.13505

Change in IL-2 Receptor A

	Secukinumab	Placebo
Number of Participants Analyzed [units:	46	45

participants]		
Change in IL-2 Receptor A (units: pg/mL) Mean ± Standard Deviation		
Baseline	25.5554 ± 59.47232	21.0665 ± 61.46295
Change from Baseline at Week 12	-3.3606 ± 38.52458	-1.1162 ± 6.31189

Change in IL-18

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in IL-18 (units: pg/mL) Mean ± Standard Deviation		
Baseline	1259.45 ± 1910.327	1308.47 ± 2454.672
Change from Baseline at Week 12	34555.1 ± 231199.6	-627.77 ± 1874.377

Change in IL-6

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in IL-6 (units: pg/mL) Mean ± Standard Deviation		
Baseline	5.6477 ±	1.6658 ±

	20.81242	1.50954
Change from Baseline at Week 12	0.1334 ± 29.35524	-0.0900 ± 1.78692

Change in Intermediate-Density Lipoprotein (IDL) Particle

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in Intermediate-Density Lipoprotein (IDL) Particle (units: nmol/mL) Mean ± Standard Deviation		
Baseline	284.350 ± 179.6482	271.049 ± 155.7413
Change from Baseline at Week 12	47.0500 ± 167.6253	2.3902 ± 160.6046

Change LDL Cholesterol

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change LDL Cholesterol (units: mg/dL) Mean ± Standard Deviation		
Baseline	122.475 ± 28.86040	121.049 ± 36.39708
Change from Baseline at Week 12	9.9750 ± 29.84532	-6.2927 ± 34.42401

Change in Leptin

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in Leptin (units: pg/mL) Mean ± Standard Deviation		
Baseline	19913.4 ± 21835.66	36813.3 ± 62138.25
Change from Baseline at Week 12	-1886.0 ± 11701.00	-5595.9 ± 17042.08

LDL Particle Total

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
LDL Particle Total (units: nmol/L) Mean ± Standard Deviation		
Baseline	1236.35 ± 317.9542	1263.00 ± 447.3457
Change from Baseline at Week 12	114.250 ± 294.8695	-111.39 ± 343.2109

LDL size

	Secukinumab	Placebo
Number of Participants Analyzed [units:	46	45

participants]		
LDL size (units: nm) Mean ± Standard Deviation		
Baseline	21.2200 ± 0.74977	21.1171 ± 0.76384
Change from Baseline at Week 12	-0.0025 ± 0.70036	0.1439 ± 0.53807

Change in Triglycerides

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in Triglycerides (units: mg/dL) Mean ± Standard Deviation		
Baseline	123.200 ± 52.90398	125.293 ± 79.10633
Change from Baseline at Week 12	11.5000 ± 62.56279	-10.732 ± 60.25281

Change in TNF-α

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change in TNF-α (units: pg/mL) Mean ± Standard Deviation		
Baseline	2.3919 ±	2.8089 ±

	1.79049	4.11492
Change from Baseline at Week 12	-0.3577 ± 1.52948	-0.9818 ± 3.85715

Change VLDL Particle Total

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Change VLDL Particle Total (units: nmol/L) Mean ± Standard Deviation		
Baseline	52.9125 ± 26.92102	54.5829 ± 27.57024
Change from Baseline at Week 12	3.2500 ± 28.56421	3.2024 ± 25.40299

VLDL size

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
VLDL size (units: nm) Mean ± Standard Deviation		
Baseline	51.5650 ± 9.11152	50.1195 ± 9.51641
Change from Baseline at Week 12	-0.3950 ± 9.30271	-0.7927 ± 7.72572

Area and Severity Index 75 (PASI 75)

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45
Area and Severity Index 75 (PASI 75) (units: percentage of participants)		
week 12	84.8	0.0

Psoriasis Area and Severity Index 90 (PASI 90)

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	47
Psoriasis Area and Severity Index 90 (PASI 90) (units: percentage of participants)		
week 12	73.9	0.0

Psoriasis Area and Severity Index 100 (PASI100)

	Secukinumab	Placebo
Number of Participants Analyzed [units: participants]	46	45

Psoriasis Area and Severity Index 100 (PASI100) (units: percentage of participants)		
week 12	37.0	0.0

Investigator's Global Assessment modified 2011 (IGA mod 2011) score of 0 or 1

	Secukinumab	**Placebo**
Number of Participants Analyzed [units: participants]	46	45
Investigator's Global Assessment modified 2011 (IGA mod 2011) score of 0 or 1 (units: percentage of participants)		
week 12	78.3	0.0

Dermatology Life Quality Index (DLQI) total score

	Secukinumab	**Placebo**
Number of Participants Analyzed [units: participants]	46	45
Dermatology Life Quality Index (DLQI) total score (units: scores on a scale) Mean ± Standard Deviation		
Baseline	12.30 ± 7.65	12.6 ± 7.21

Change from baseline at Week 12	-9.4 ± 7.91	-0.5 ± 3.97

Summary of Safety

Safety Results

All-Cause Mortality

	Secukinumab 300 mg N = 46	Placebo/Secukinumab 300 mg N = 45	Total N = 91
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) were collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 48 weeks
Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment

	Secukinumab 300 mg N = 46	Placebo/Secukinumab 300 mg N = 45	Total N = 91

Total participants affected	5 (10.87%)	0 (0.00%)	5 (5.49%)
Gastrointestinal disorders			
Abdominal pain	1 (2.17%)	0 (0.00%)	1 (1.10%)
Injury, poisoning and procedural complications			
Rib fracture	1 (2.17%)	0 (0.00%)	1 (1.10%)
Upper limb fracture	1 (2.17%)	0 (0.00%)	1 (1.10%)
Musculoskeletal and connective tissue disorders			
Muscular weakness	1 (2.17%)	0 (0.00%)	1 (1.10%)
Vascular disorders			
Aortic stenosis	1 (2.17%)	0 (0.00%)	1 (1.10%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) were collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 48 weeks
Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Secukinumab 300 mg	**Placebo/Secukinumab 300 mg**	**Total N = 91**

	N = 46	N = 45	
Total participants affected	21 (45.65%)	18 (40.00%)	39 (42.86%)
Gastrointestinal disorders			
Diarrhoea	3 (6.52%)	2 (4.44%)	5 (5.49%)
Infections and infestations			
Bronchitis	3 (6.52%)	0 (0.00%)	3 (3.30%)
Nasopharyngitis	9 (19.57%)	7 (15.56%)	16 (17.58%)
Sinusitis	0 (0.00%)	3 (6.67%)	3 (3.30%)
Upper respiratory tract infection	6 (13.04%)	4 (8.89%)	10 (10.99%)
Musculoskeletal and connective tissue disorders			
Arthralgia	5 (10.87%)	3 (6.67%)	8 (8.79%)
Nervous system disorders			
Dizziness	1 (2.17%)	3 (6.67%)	4 (4.40%)
Headache	0 (0.00%)	4 (8.89%)	4 (4.40%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (2.17%)	4 (8.89%)	5 (5.49%)

Conclusion:

This clinical study evaluated the effect of secukinumab compared to placebo on aortic vascular inflammation with respect to the change from baseline in the TBR from the aorta. All patients enrolled in the study were psoriasis patients ≥ 18 years

of age with a clinical diagnosis of moderate to severe plaque psoriasis of at least 6 months prior to randomization. Patients were treated with either 300 mg secukinumab or placebo for 12 weeks, followed by Treatment Period 2 lasting 40 weeks where all patients were treated with secukinumab.

The primary efficacy variable was the change from baseline in the TBR from the whole aorta obtained via FDG-PET/CT scans. The primary analysis time point was at Week 12. No statistically significant differences were observed between patients treated with secukinumab and patients treated with placebo.

No clear differences between treatment groups were seen in most cardiometabolic biomarkers at Week 12. However, there were several notable exceptions. Patients treated with secukinumab had statistically significantly higher cholesterol, LDL cholesterol, and LDL cholesterol particle size compared to patients with placebo.

Patients treated with secukinumab had a significant improvement at week 12 in their significantly better at Week 12 on the PASI 75, PASI 90, PASI 100, IGA mod 2011, and DLQI compared to patients treated with placebo. When all patients were treated with secukinumab after Week 12, patients treated with placebo then secukinumab rapidly improved their response on these assessments in a matter of weeks.

Secukinumab was safe to use and well tolerated in general. While the overall incidence of adverse events was slightly higher in the patients treated with secukinumab compared to patients treated with placebo, no clear differences could be distinguished in any system organ class or preferred term. The majority of AEs in both treatment groups were mild in severity. More treatment related AEs were identified in patients treated with secukinumab only. No differences were seen between treatment groups in any clinical hematology assay, any clinical chemistry laboratory assay, or any examination of vital signs.

There were no deaths in the study. Five SAEs were reported in patients treated with secukinumab. Four patients treated with secukinumab and 1 patient treated with placebo/secukinumab had study treatment discontinuation due to AEs.
Overall, while secukinumab was efficacious in treating plaque psoriasis as expected, it had a neutral impact on aortic vascular inflammation with minimal to no effect on cardiometabolic biomarkers. There was a slight elevation in cholesterol level, however, this was not deemed clinically significant by the investigators.

Date of Clinical Trial Report

12 February 2019