NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Secukinumab

Trial Indication

moderate to severe chronic plaque psoriasis

Protocol Number

CAIN457A2326

Protocol Title

A 52-week, randomized, double-blind study of secukinumab (300 mg) compared to ustekinumab in subjects with moderate to severe plaque psoriasis

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase IIIb

Study Start/End Dates

Study Start Date: June 2016 (Actual)
Primary Completion Date: July 2018 (Actual)
Study Completion Date: July 2018 (Actual)

Study Design/Methodology

This was a multicenter, randomized, double-blind, active-controlled, parallel-group trial in patients with moderate to severe chronic plaque-type psoriasis. Eligible patients were randomized in a 1:1 ratio to one of the two double-blind treatment groups: secukinumab 300 mg s.c. and ustekinumab 45 mg or 90 mg s.c. (depending upon body weight at randomization).

Centers

163 centers in 11 countries: United States (131), Canada(4), Iceland(1), Slovakia (Slovak Republic)(2), Korea, Republic of (6), Malaysia (2), Hungary (3), Guatemala (3), Poland (7), Vietnam (2), Czech Republic (2)

Objectives:

Primary objectives: The co-primary objectives were to demonstrate the superiority of secukinumab compared to ustekinumab in patients with moderate to severe plaque psoriasis with respect to both PASI 90 and IGA mod 2011 0 or 1 response at Week 12.

Secondary objectives:
Secondary objectives were to demonstrate the superiority of secukinumab compared to ustekinumab in patients with moderate to severe plaque psoriasis with respect to: PASI 75 response at Week 4, 12, and 16, PASI 90 at Week 16 and Week 52, PASI 100 at Week 12 and Week 16 and IGA mod 2011 0 or 1 at Week 16. Other secondary objectives were to investigate the clinical safety of secukinumab compared to ustekinumab as assessed by adverse event (AE) monitoring, vital signs, and clinical laboratory variables.

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

- Secukinumab for s.c. injection was provided in a pre-filled syringe containing 150 mg secukinumab. Each 300 mg dose was given as two s.c. injections of 150 mg.

- Secukinumab placebo: secukinumab placebo to 150 mg secukinumab for s.c. injection was provided in a matching pre-filled syringe. Each pre-filled syringe contained a mixture of inactive excipients, matching the composition of the secukinumab 150 mg dose.

- Ustekinumab was provided in a pre-filled syringe containing 45 mg of ustekinumab for s.c. injection. Patients weighing >100 kg at Baseline received a dose of 90 mg according to the label, which consisted of two 45 mg pre-filled syringes.

Statistical Methods

The co-primary endpoints of this study were the proportion of patients with IGA mod 2011 (0 or 1) response and a PASI 90 response at Week 12 with secukinumab compared with ustekinumab. The statistical hypothesis was that secukinumab is not superior to ustekinumab in the proportion of patients with IGA mod 2011 (0 or 1) and or PASI 90 response and at Week 12.

The efficacy variables were analyzed analogously to the primary endpoints at Week 12. i.e., the logistic regression model with treatment group, baseline body weight strata and baseline PASI score as exploratory variables. Odds ratio were computed for comparison of secukinumab versus ustekinumab utilizing the logistic regression model fitted. Missing data was handled by multiple imputation method. A sequentially hierarchical testing procedure was used, and such that a family-wise type I error of alpha = 2.5% was kept.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

• Subjects must give a written, signed and dated informed consent
• Chronic plaque-type psoriasis present for at least 6 months before randomization
• Moderate to severe plaque psoriasis as defined at randomization by:
    PASI score of ≥12 and
    Body Surface Area (BSA) affected by plaque-type psoriasis ≥10% and
    IGA mod 2011 ≥3 (based on a scale of 0–4)
• Candidate for systemic therapy, defined as having psoriasis inadequately controlled by:
    Topical treatment (including topical corticosteroids) and/or

Phototherapy and/or
Previous systemic therapy

Exclusion Criteria

• Forms of psoriasis other than plaque psoriasis
• Drug-induced psoriasis
• Ongoing use of prohibited treatments
• Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA, or ustekinumab, or any therapies targeting IL-12 or IL-23
• Use of any other investigational drugs within 5 half-lives of the investigational treatment before study drug initiation
• Pregnant or nursing (lactating) women

Participant Flow Table

Overall Study

	Secukinumab 2 x 150mg s.c. PFS	Ustekinumab 45mg or 90 mg s.c. PFS	Total
Arm/Group Description	Secukinumab 300mg s.c. injection in 2 150mg pre-fiilled syringes	Ustekinumab s.c. 45 mg or 90 mg (2x 45mg) depending on body weight in pre-filled syringes	
Started	550	552	1102
Completed	489	488	977
Not Completed	61	64	125
Adverse Event	17	9	26
Lack of Efficacy	4	9	13
Lost to Follow-up	13	12	25
Noncompliance with treatment	0	2	2
Physician Decision	1	7	8
Pregnancy	1	2	3

Protocol Violation	3	3	6
Withdrawal by Subject	20	19	39
Death	2	0	2
New therapy for study indication	0	1	1

Baseline Characteristics

	Secukinumab 2 x 150mg s.c. PFS	Ustekinumab 45 mg or 90 mg PFS	Total
Arm/Group Description	Secukinumab 300mg s.c. injection in 2 150mg pre-filled syringes	Ustekinumab s.c. 45 mg or 90 mg (2x 45 mg) depending on body weight in pre-filled syringes	
Number of Participants [units: participants]	550	552	1102
Age Continuous[1] (units: years) Mean ± Standard Deviation			
	45.4±14.09	45.3±14.16	45.4±14.12
Sex: Female, Male Count of Participants			
Female	194	176	370
Male	356	376	732
Race/Ethnicity, Customized Count of Participants			
Caucasian	416	410	826
Black	21	24	45
Asian	60	57	117
Native American	34	41	75

Pacific Islander	1	5	6
Unknown	4	2	6
Other	14	13	27
Age, Customized (units:) Count of Participants (Not Applicable)			
<65 years	488	494	982
>=65 years	62	58	120
>=75 years	2	10	12

[1] average age of participants

Summary of Efficacy

Primary Outcome Results

Participants who achieved Psoriasis Area and Severity Index (PASI) 90 AT WEEK 12

(Time Frame: Week 12)

	Secukinumab 2 x 150mg s.c. PFS	Ustekinumab 45mg or 90 mg PFS
Arm/Group Description	Secukinumab 300mg s.c. injection in 2 150mg pre-filled syringes	Ustekinumab s.c. 45 mg or 90 mg (2x 45 mg) depending on body weight in pre-filled syringes
Number of Participants Analyzed [units: participants]	550	552
Participants who achieved Psoriasis Area and Severity Index (PASI) 90 AT WEEK 12 Count of Participants		
	366	265

Statistical Analysis

Groups	Secukinumab 2 x 150mg s.c. PFS, Ustekinumab 45mg or 90 mg PFS
P Value	<0.0001
Method	Regression, Logistic
Odds Ratio (OR)	2.21
95 % Confidence Interval 2-Sided	1.72 to 2.84

Participants with IGA mod 2011 0 or 1 AT WEEK 12

(Time Frame: Week 12)

	Secukinumab 2 x 150mg s.c. PFS	Ustekinumab 45mg or 90 mg PFS
Arm/Group Description	Secukinumab 300mg s.c. injection in 2 150mg pre-filled syringes	Ustekinumab s.c. 45 mg or 90 mg (2x 45 mg) depending on body weight in pre-filled syringes
Number of Participants Analyzed	550	552
Participants with IGA mod 2011 0 or 1 AT WEEK 12 Count of Participants		
	397	306

Statistical Analysis

Groups	Secukinumab 2 x 150mg s.c. PFS, Ustekinumab 45mg or 90 mg PFS
P Value	<0.0001
Method	Regression, Logistic

Odds Ratio (OR)	2.10
95% Confidence Interval 2-Sided	1.63 to 2.72

Logistic regression analysis of IGA mod 2011 0 or 1, PASI 75, PASI 90 and PASI 100 response at Week 4, Week 12, Week 16, and Week 52 (multiple imputation) (FAS)

Visit	Response criteria	AIN457 300 mg N=550 n*/m (%)	UST 45/90 mg N=552 n*/m (%)	Odds ratio estimate (95% CI)	One-sided p-value
Week 4	IGA 0 or 1	149/550 (27.0)	43/552 (7.8)	4.60 (3.17, 6.66)	<0.0001
	PASI 75	221/550 (40.2)	90/552 (16.4)	3.53 (2.65, 4.71)	<0.0001
	PASI 90	92/550 (16.7)	22/552 (4.0)	5.00 (3.07, 8.13)	<0.0001
	PASI 100	32/550 (5.7)	4/552 (0.7)	8.40 (2.94, 24.03)	<0.0001
Week 12	IGA 0 or 1	397/550 (72.3)	306/552 (55.5)	2.10 (1.63, 2.72)	<0.0001
	PASI 75	484/550 (88.1)	409/552 (74.1)	2.62 (1.89, 3.62)	<0.0001
	PASI 90	366/550 (66.5)	265/552 (47.9)	2.21 (1.72, 2.84)	<0.0001
	PASI 100	210/550 (38.1)	111/552 (20.1)	2.50 (1.89, 3.31)	<0.0001
Week 16	IGA 0 or 1	432/550 (78.6)	326/552 (59.1)	2.57 (1.96, 3.37)	<0.0001
	PASI 75	506/550 (91.9)	441/552 (80.0)	2.86 (1.96, 4.17)	<0.0001
	PASI 90	423/550 (76.9)	299/552 (54.1)	2.85 (2.19, 3.71)	<0.0001
	PASI 100	250/550 (45.5)	147/552 (26.7)	2.33 (1.80, 3.01)	<0.0001
Week 52	IGA 0 or 1	418/550 (76.0)	332/552 (60.2)	2.12 (1.61, 2.79)	<0.0001
	PASI 75	489/550 (89.0)	453/552 (82.1)	1.74 (1.21, 2.50)	0.0013
	PASI 90	402/550 (73.2)	330/552 (59.8)	1.84 (1.41, 2.41)	<0.0001
	PASI 100	269/550 (48.9)	185/552 (33.5)	1.92 (1.48, 2.47)	<0.0001

Summary of Safety

Safety Results

All-Cause Mortality

	AIN457 300 mg N = 550	UST 45 or 90 mg N = 552	All Patients N = 1102
Arm/Group Description	Secukinumab 300mg s.c. injection in 2 150mg pre-filled syringes	Ustekinumab s.c. 45 mg or 90 mg (2x 45 mg) depending on body weight in pre-filled syringes	All Patients
Total participants affected	2 (0.36%)	0 (0.00%)	2 (0.18%)

Serious Adverse Events by System Organ Class

Time Frame	AEs and SAEs were collected for the maximum duration of treatment and follow up for a participant per protocol for approximately x months. All-cause mortality (deaths) was collected from First Patient First Visit (FPFV) to Last Patient Last Visit (LPLV) up to a maximum of 52 weeks
Additional Description	All-cause mortality (deaths) was collected for as long as participants could be contacted from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV) up to a maximum of 52 weeks
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

	AIN457 300 mg N = 550	UST 45 or 90 mg N = 552	All Patients N = 1102
Arm/Group Description	Secukinumab 300mg s.c. injection in 2 150mg pre-filled syringes	Ustekinumab s.c. 45 mg or 90 mg (2x 45mg) depending on body weight in pre-filled syringes	All Patients

Total participants affected	29 (5.27%)	21 (3.80%)	50 (4.54%)
Blood and lymphatic system disorders			
Lymphadenopathy	1 (0.18%)	0 (0.00%)	1 (0.09%)
Cardiac disorders			
Angina pectoris	1 (0.18%)	0 (0.00%)	1 (0.09%)
Atrial fibrillation	3 (0.55%)	0 (0.00%)	3 (0.27%)
Myocardial ischaemia	1 (0.18%)	0 (0.00%)	1 (0.09%)
Ventricular tachycardia	2 (0.36%)	0 (0.00%)	2 (0.18%)
Gastrointestinal disorders			
Anal fissure	1 (0.18%)	0 (0.00%)	1 (0.09%)
Colitis erosive	1 (0.18%)	0 (0.00%)	1 (0.09%)
Colitis ulcerative	1 (0.18%)	0 (0.00%)	1 (0.09%)
Haemorrhoids	0 (0.00%)	1 (0.18%)	1 (0.09%)
Pancreatitis acute	1 (0.18%)	0 (0.00%)	1 (0.09%)
General disorders and administration site conditions			
Sudden cardiac death	1 (0.18%)	0 (0.00%)	1 (0.09%)
Hepatobiliary disorders			
Cholecystitis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Immune system disorders			
Anaphylactic reaction	1 (0.18%)	0 (0.00%)	1 (0.09%)
Drug hypersensitivity	0 (0.00%)	1 (0.18%)	1 (0.09%)

Infections and infestations			
Bronchitis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Cellulitis	1 (0.18%)	2 (0.36%)	3 (0.27%)
Clostridium difficile colitis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Dengue fever	2 (0.36%)	0 (0.00%)	2 (0.18%)
Diverticulitis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Endocarditis	0 (0.00%)	1 (0.18%)	1 (0.09%)
Peritonitis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Pharyngitis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Pneumonia streptococcal	1 (0.18%)	0 (0.00%)	1 (0.09%)
Pyelonephritis acute	0 (0.00%)	1 (0.18%)	1 (0.09%)
Sepsis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Skin candida	1 (0.18%)	0 (0.00%)	1 (0.09%)
Tonsillitis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Urinary tract infection	0 (0.00%)	1 (0.18%)	1 (0.09%)
Injury, poisoning and procedural complications			
Comminuted fracture	0 (0.00%)	1 (0.18%)	1 (0.09%)
Fall	0 (0.00%)	1 (0.18%)	1 (0.09%)
Gun shot wound	0 (0.00%)	1 (0.18%)	1 (0.09%)
Incisional hernia	1 (0.18%)	0 (0.00%)	1 (0.09%)
Postoperative ileus	1 (0.18%)	0 (0.00%)	1 (0.09%)
Toxicity to various agents	1 (0.18%)	0 (0.00%)	1 (0.09%)

Wrist fracture	0 (0.00%)	1 (0.18%)	1 (0.09%)
Investigations			
Haemoglobin decreased	0 (0.00%)	1 (0.18%)	1 (0.09%)
Metabolism and nutrition disorders			
Dehydration	0 (0.00%)	1 (0.18%)	1 (0.09%)
Hyperglycaemia	0 (0.00%)	1 (0.18%)	1 (0.09%)
Musculoskeletal and connective tissue disorders			
Bursitis	0 (0.00%)	1 (0.18%)	1 (0.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma	0 (0.00%)	1 (0.18%)	1 (0.09%)
Basal cell carcinoma	0 (0.00%)	1 (0.18%)	1 (0.09%)
Invasive ductal breast carcinoma	0 (0.00%)	1 (0.18%)	1 (0.09%)
Laryngeal squamous cell carcinoma	1 (0.18%)	0 (0.00%)	1 (0.09%)
Squamous cell carcinoma of lung	1 (0.18%)	0 (0.00%)	1 (0.09%)
Squamous cell carcinoma of the oral cavity	0 (0.00%)	1 (0.18%)	1 (0.09%)
T-cell lymphoma	0 (0.00%)	1 (0.18%)	1 (0.09%)
Nervous system disorders			
Cerebrovascular accident	0 (0.00%)	1 (0.18%)	1 (0.09%)

Ischaemic stroke	0 (0.00%)	1 (0.18%)	1 (0.09%)
Loss of consciousness	0 (0.00%)	1 (0.18%)	1 (0.09%)
Syncope	0 (0.00%)	1 (0.18%)	1 (0.09%)
Product issues			
Device inappropriate shock delivery	1 (0.18%)	0 (0.00%)	1 (0.09%)
Psychiatric disorders			
Depression	0 (0.00%)	1 (0.18%)	1 (0.09%)
Psychotic disorder	1 (0.18%)	0 (0.00%)	1 (0.09%)
Renal and urinary disorders			
Acute kidney injury	1 (0.18%)	0 (0.00%)	1 (0.09%)
Nephrolithiasis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Renal infarct	0 (0.00%)	1 (0.18%)	1 (0.09%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	3 (0.55%)	0 (0.00%)	3 (0.27%)
Asthma	1 (0.18%)	0 (0.00%)	1 (0.09%)
Pulmonary embolism	1 (0.18%)	0 (0.00%)	1 (0.09%)
Pulmonary thrombosis	1 (0.18%)	0 (0.00%)	1 (0.09%)
Skin and subcutaneous tissue disorders			
Drug eruption	1 (0.18%)	0 (0.00%)	1 (0.09%)
Toxic skin eruption	0 (0.00%)	1 (0.18%)	1 (0.09%)
Vascular disorders			

Deep vein thrombosis	2 (0.36%)	1 (0.18%)	3 (0.27%)
Orthostatic hypotension	0 (0.00%)	1 (0.18%)	1 (0.09%)

Other Adverse Events by System Organ Class

Time Frame	AEs and SAEs were collected for the maximum duration of treatment and follow up for a participant per protocol for approximately 52 weeks. All-cause mortality (deaths) was collected from First Patient First Visit (FPFV) to Last Patient Last Visit (LPLV) up to a maximum of 52 weeks
Additional Description	All-cause mortality (deaths) was collected for as long as participants could be contacted from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV) up to a maximum of 52 weeks
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	AIN457 300 mg N = 550	**UST 45 or 90 mg N = 552**	**All Patients N = 1102**
Arm/Group Description	Secukinumab 300mg s.c. injection in 2 150mg pre-filled syringes	Ustekinumab s.c. 45 mg or 90 mg in two 45 mg pre-filled syringes depending on body weight	All Patients
Total participants affected	216 (39.27%)	229 (41.49%)	445 (40.38%)
Gastrointestinal disorders			
Diarrhoea	26 (4.73%)	24 (4.35%)	50 (4.54%)
Nausea	6 (1.09%)	13 (2.36%)	19 (1.72%)
Infections and infestations			
Bronchitis	8 (1.45%)	18 (3.26%)	26 (2.36%)

Conjunctivitis	12 (2.18%)	6 (1.09%)	18 (1.63%)
Nasopharyngitis	55 (10.00%)	54 (9.78%)	109 (9.89%)
Sinusitis	25 (4.55%)	18 (3.26%)	43 (3.90%)
Upper respiratory tract infection	49 (8.91%)	61 (11.05%)	110 (9.98%)
Urinary tract infection	13 (2.36%)	9 (1.63%)	22 (2.00%)
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (1.64%)	14 (2.54%)	23 (2.09%)
Back pain	14 (2.55%)	20 (3.62%)	34 (3.09%)
Nervous system disorders			
Headache	26 (4.73%)	25 (4.53%)	51 (4.63%)
Respiratory, thoracic and mediastinal disorders			
Cough	17 (3.09%)	16 (2.90%)	33 (2.99%)
Oropharyngeal pain	14 (2.55%)	17 (3.08%)	31 (2.81%)
Skin and subcutaneous tissue disorders			
Dermatitis contact	12 (2.18%)	8 (1.45%)	20 (1.81%)
Pruritus	12 (2.18%)	18 (3.26%)	30 (2.72%)
Vascular disorders			
Hypertension	17 (3.09%)	22 (3.99%)	39 (3.54%)

Conclusion:

This study demonstrated that secukinumab is superior to ustekinumab in clearing skin of patients with moderate to severe plaque psoriasis, with superior efficacy up to one year including speed of onset, and a greater improvement in patients' health-related quality of life while maintaining a comparable safety profile.

Date of Clinical Trial Report

11 December 2018