Sponsor
Novartis

Generic Drug Name
Secukinumab

Trial Indication(s)
Moderate-to-severe plaque psoriasis

Protocol Number
CAIN457A2110

Protocol Title
An open-label, single sequence crossover study investigating the influence of secukinumab treatment on the pharmacokinetics of midazolam as a CYP3A4 substrate in patients with moderate-to-severe plaque psoriasis.

Clinical Trial Phase
Phase I

Phase of Drug Development
Phase IV

Study Start/End Dates
Study Start Date (FPFV): 17 Dec 2015
Study End Date (LPLV): 11 Jan 2017

Reason for Termination (If applicable)
Not applicable for this trial.

Study Design/Methodology

This was an open-label, single sequence crossover, confirmatory study investigating potential disease-drug-drug interaction of secukinumab in male and female patients with moderate-to-severe plaque psoriasis. Secukinumab 300 mg was administered subcutaneously as weekly injections at Weeks 0, 1, 2, 3 and 4, followed by every 4 weeks thereafter (until Week 24). Midazolam 5 mg was given orally at Baseline, Days 8 (Week 1) and 36 (Week 5).

Centers

8 centers in the USA

Objectives:

Primary objective: to investigate the effect of secukinumab on the pharmacokinetics (PK) of midazolam (probe substrate for CYP3A4) in patients with moderate-to-severe plaque psoriasis.
Endpoint: Midazolam Cmax, AUC0-12h, AUClast and AUCinf
Secondary objective: to evaluate the overall safety and tolerability of 24 week administration of secukinumab and of the co-administration of midazolam and secukinumab in patients with moderate-to-severe plaque psoriasis.

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

Test product: Secukinumab 300 mg (2 × 150 mg/mL pre-filled syringes) was administered subcutaneously as weekly injections at Weeks 0, 1, 2, 3 and 4, followed by every 4 weeks thereafter (until Week 24).
Reference therapy: Midazolam HCl oral syrup (e.g. 2 mg/mL cherry-flavored midazolam syrup, Roxane Laboratories, Columbus, Ohio) was provided by the study sites. Midazolam 5 mg was given orally at Baseline, Days 8 (Week 1) and 36 (Week 5).

Statistical Methods

The sample size calculation was based on the primary objective to investigate the effect of secukinumab on the PK of midazolam (probe substrate for CYP3A4) in patients with moderate-to-severe plaque psoriasis. A total of 25 patients were recruited in order to obtain 20 completers in this study considering 25% drop out. The sample size of 20 complete patients provided greater than 90% power to detect a 50% decrease in midazolam PK parameters Cmax and AUC on Day 8 (Week 1) and Day 36 (Week 5) as compared to Baseline. The calculation was based on an assumed conservative CV% of 30% for Cmax and AUC of midazolam, chosen from the results of a previous Novartis trial and literature data. Descriptive statistics were calculated for all plasma concentrations and pharmacokinetic parameters of midazolam. Analysis of primary variables included AUC0-12h, AUCinf, and Cmax of midazolam analytes in plasma. The effect of secukinumab on the PK of midazolam (probe substrate for CYP3A4) in patients with moderate-to-severe plaque psoriasis was analyzed by a fixed effect model. Log transformed PK parameters, Cmax, AUC0-12h and AUCinf of midazolam, were analyzed using a fixed effect model with day as fixed and subject as random effect. The difference in adjusted means along with 90% confidence intervals was calculated for the contrast Day 8 (Week 1(Test)) and Day 36 (Week 5 (Test)) vs Baseline (Reference).

The results were back transformed to the original scale to obtain adjusted geometric mean ratios (Day 8 vs Baseline; Day 36 vs Baseline) and the corresponding 90% confidence intervals. An interim analysis (IA) of Week 5 (Day 36) data (PK of midazolam and safety) was planned and conducted. The interim CSR was prepared for submission to FDA after all patients had Week 5 data. No study design changes were made based on the Week 5 IA.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Moderate to severe plaque psoriasis as defined at Baseline by PASI score of 12 or greater; IGA modified 2011 score of 3 or greater (based on a scale of 0 – 4) and Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater.
- Candidate for systemic therapy, defined as having chronic plaque-type psoriasis considered inadequately controlled by topical treatment and/or, phototherapy and/or previous systemic therapy.
- Men or women at least 18 years of age at time of screening, required to understand and communicate with the Investigator and comply with the requirements of the study and were required to give a written, signed and dated informed consent before any study related activity was performed.

Exclusion criteria:

- Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis); drug-induced psoriasis.
- Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor.
- Pregnant or nursing (lactating) women.
- History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection. Past medical history record of HIV, chronic hepatitis B or chronic hepatitis C.
- Use of any prescription drug or OTC medication, herbal remedy or nutrient that has a known history of drug interactions with CYP3A4 within 2 months prior to dosing.
- Patients with known history of hypersensitivity to midazolam.
- Use of investigational treatments within 4 weeks before randomization, or within a period of 5 half-lives of the investigational treatment, whichever was longer.

Participant Flow Table

Patient disposition - n (%) of patients (Safety analysis set)

Disposition Reason	Secukinumab 300 mg + Midazolam 5 mg N=24 n (%)
Completed	20 (83.3)
Discontinued	4 (16.7)
Primary reason for discontinuation	
Adverse Event(s)[1]	1 (4.2)
Unsatisfactory therapeutic effect	1 (4.2)
Lost to follow-up	1 (4.2)
Patient/guardian decision	1 (4.2)

[1] 1 patient discontinued from the study due to drug abuse, which was entered in the eCRF as 'discontinuation due to AE'

Baseline Characteristics

Patient demographics (Safety analysis set)

Characteristic	Secukinumab 300 mg + Midazolam 5 mg N=24
Age (years) [1]	
Mean (SD)	44.3 (11.78)
Median	45.0
Range	18 – 68
Sex -n (%)	
Male	13 (54.2)
Female	11 (45.8)

Characteristic	Secukinumab 300 mg + Midazolam 5 mg N=24
Race -n (%)	
Caucasian	21 (87.5)
Black	1 (4.2)
Asian	1 (4.2)
Other	1 (4.2)
Ethnicity -n (%)	
Hispanic/Latino	9 (37.5)
Indian (Indian subcontinent)	1 (4.2)
Mixed Ethnicity	1 (4.2)
Other	13 (54.2)
Weight (kg) [2]	
Mean (SD)	100.33 (22.238)
Median	99.10
Range	69.2 - 159.3
Height (cm)	
Mean (SD)	171.93 (8.517)
Median	172.60
Range	153.5 - 188.0
Body mass index (kg/m^2) [3]	
Mean (SD)	33.94 (7.116)
Median	33.05
Range	25.3 - 52.0

[1] Age is calculated from date of screening and date of birth.

[2] Weight and height are taken from screening vital signs evaluations.

[3] BMI: Body mass index calculated based on raw data measurements

Summary of Efficacy

Primary Outcome Result(s)

Summary statistics of Midazolam plasma PK parameter values (PK analysis set)

Profile day	Statistic	Cmax (ng/mL)	AUC0-12h (h*ng/mL)	AUCinf (h*ng/mL)	T1/2 (h)	Tmax * (h)	Vz/F (L)	CL/F (L/h)
Baseline	n	22	22	22	22	22	22	22
	Mean (SD)	26.2 (9.31)	77.0 (30.6)	88.1 (35.4)		0.500 [0.250;1.97]	444 (243)	64.9 (22.9)
	CV% mean	35.5	39.7	40.2	32.8	60.6	54.8	35.4
Day 8	n	22	22	21	21	22	21	21
	Mean (SD)	29.3 (12.4)	74.2 (31.2)	87.1 (39.7)	4.82 (1.50)	0.492 [0.217;3.00]	440 (159)	65.2 (19.6)
	CV% mean	42.3	42.0	45.6	31.2	109.6	36.2	30.1
Day 36	n	21	21	20	21	21	20	20
	Mean (SD)	25.5 (11.4)	70.5 (23.2)	84.0 (27.8)	4.82 (1.43)	0.567 [0.233;2.07]	436 (158)	66.9 (25.6)
	CV% mean	44.8	33.0	33.1	29.6	70.5	36.2	38.2

* Median and range is given for Tmax

CV% = coefficient of variation (%) = (sd/mean)*100;

Geometric mean ratio (Midazolam and secukinumab/Midazolam) and 90% confidence intervals for PK parameters (PK analysis set)

Parameter	Visit	n*	Adjusted geometric mean	Comparison (Day/baseline)	Geometric mean ratio	90% CI for ratio
AUC0-12h (h*ng/mL)	Baseline	22	71.84			
	Day 8	22	69.90	Day 8 vs Baseline	0.97	(0.87, 1.09)
	Day 36	21	67.11	Day 36 vs Baseline	0.93	(0.83, 1.05)
AUCinf (h*ng/mL)	Baseline	22	82.17			
	Day 8	21	81.70	Day 8 vs Baseline	0.99	(0.88, 1.12)
	Day 36	20	79.35	Day 36 vs Baseline	0.97	(0.85, 1.09)

Parameter	Visit	n*	Adjusted geometric mean	Comparison (Day/baseline)	Geometric mean ratio	90% CI for ratio
Cmax (ng/mL)	Baseline	22	24.81			
	Day 8	22	27.13	Day 8 vs Baseline	1.09	(0.94, 1.28)
	Day 36	21	23.26	Day 36 vs Baseline	0.94	(0.80, 1.10)

*n = number of patients with non-missing values. The log transformed primary PK parameters of Cmax, AUC_{0-12} and AUC_{inf} were analyzed using a mixed effect model with day as fixed and patients as random effect. Midazolam 5 mg was administered on Baseline (Reference), Day 8 (Test) and Day 36 (Test)

Secondary Outcome Result(s)

Refer to the Safety Result section for secondary outcome result.

Summary of Safety

Safety Results

Incidence of AEs by primary system organ class - n (%) of patients (Safety set)

Primary system organ class	Midazolam 5 mg alone (Baseline) N=24 n (%)	Secukinumab 300 mg + Midazolam 5 mg (Post-Baseline) N=24 n (%)	All treatments N=24 n (%)
Number of patients with at least one AE	1 (4.2)	16 (66.7)	16 (66.7)
Infections and infestations	0	6 (25.0)	6 (25.0)
Musculoskeletal and connective tissue disorders	0	3 (12.5)	3 (12.5)
Nervous system disorders	0	3 (12.5)	3 (12.5)
Cardiac disorders	0	2 (8.3)	2 (8.3)
Gastrointestinal disorders	0	2 (8.3)	2 (8.3)

Primary system organ class	Midazolam 5 mg alone (Baseline) N=24 n (%)	Secukinumab 300 mg + Midazolam 5 mg (Post-Baseline) N=24 n (%)	All treatments N=24 n (%)
Injury, poisoning and procedural complications	0	2 (8.3)	2 (8.3)
Investigations	0	2 (8.3)	2 (8.3)
Metabolism and nutrition disorders	1 (4.2)	1 (4.2)	2 (8.3)
Psychiatric disorders	0	2 (8.3)	2 (8.3)
Reproductive system and breast disorders	0	2 (8.3)	2 (8.3)
Respiratory, thoracic and mediastinal disorders	0	2 (8.3)	2 (8.3)
Skin and subcutaneous tissue disorders	0	2 (8.3)	2 (8.3)
General disorders and administration site conditions	0	1 (4.2)	1 (4.2)
Hepatobiliary disorders	0	1 (4.2)	1 (4.2)
Vascular disorders	0	1 (4.2)	1 (4.2)

A patient with multiple AEs is counted only once in the “at least one AE” row. A patient with multiple AEs within a primary system organ class is counted only once for that system organ class and treatment.
Arranged by descending order of frequency in the total column.

Incidence of AEs by preferred term - n (%) of patients (Safety analysis set)

Preferred term	Midazolam 5 mg alone (Baseline) N=24 n (%)	Secukinumab 300 mg + Midazolam 5 mg (Post-Baseline) N=24 n (%)	All treatments N=24 n (%)
Number of patients with at least one AE	**1 (4.2)**	**16 (66.7)**	**16 (66.7)**
Dehydration	1 (4.2)	1 (4.2)	2 (8.3)
Headache	0	2 (8.3)	2 (8.3)

Preferred term	Midazolam 5 mg alone (Baseline) N=24 n (%)	Secukinumab 300 mg + Midazolam 5 mg (Post-Baseline) N=24 n (%)	All treatments N=24 n (%)
Abdominal abscess	0	1 (4.2)	1 (4.2)
Arthralgia	0	1 (4.2)	1 (4.2)
Atrial fibrillation	0	1 (4.2)	1 (4.2)
Back pain	0	1 (4.2)	1 (4.2)
Blood urine present	0	1 (4.2)	1 (4.2)
Cervical dysplasia	0	1 (4.2)	1 (4.2)
Cholelithiasis (Cholecystitis, see Section 12.2.2)	0	1 (4.2)	1 (4.2)
Cough	0	1 (4.2)	1 (4.2)
Drug dependence	0	1 (4.2)	1 (4.2)
Electrocardiogram T wave amplitude decreased	0	1 (4.2)	1 (4.2)
Gastroenteritis	0	1 (4.2)	1 (4.2)
Gastrooesophageal reflux disease	0	1 (4.2)	1 (4.2)
Genital cyst	0	1 (4.2)	1 (4.2)
Herpes zoster	0	1 (4.2)	1 (4.2)
Hypertension	0	1 (4.2)	1 (4.2)
Insomnia	0	1 (4.2)	1 (4.2)
Joint swelling	0	1 (4.2)	1 (4.2)
Ligament sprain	0	1 (4.2)	1 (4.2)
Migraine	0	1 (4.2)	1 (4.2)
Musculoskeletal pain	0	1 (4.2)	1 (4.2)
Nasopharyngitis	0	1 (4.2)	1 (4.2)
Nausea	0	1 (4.2)	1 (4.2)
Oedema	0	1 (4.2)	1 (4.2)

Preferred term	Midazolam 5 mg alone (Baseline) N=24 n (%)	Secukinumab 300 mg + Midazolam 5 mg (Post-Baseline) N=24 n (%)	All treatments N=24 n (%)
Otitis media	0	1 (4.2)	1 (4.2)
Palpitations	0	1 (4.2)	1 (4.2)
Pharyngitis streptococcal	0	1 (4.2)	1 (4.2)
QRS axis abnormal	0	1 (4.2)	1 (4.2)

Preferred term	Midazolam 5 mg alone (Baseline) N=24 n (%)	Secukinumab 300 mg + Midazolam 5 mg (Post-Baseline) N=24 n (%)	All treatments N=24 n (%)
Road traffic accident	0	1 (4.2)	1 (4.2)
Sinus bradycardia	0	1 (4.2)	1 (4.2)
Skin striae	0	1 (4.2)	1 (4.2)
Tonsillar hypertrophy	0	1 (4.2)	1 (4.2)
Upper respiratory tract infection	0	1 (4.2)	1 (4.2)
Urticaria	0	1 (4.2)	1 (4.2)

A patient with multiple AEs is counted only once in the “at least one AE” row
A patient with multiple AEs with the same preferred term is counted only once for that preferred term & treatment
AEs by preferred terms are arranged in descending order of frequency (in total group).

Overall incidence of AEs - number of events and number of subjects (Safety analysis set)

	Midazolam 5 mg alone (Baseline) N=24 nS (%) nE	Secukinumab 300 mg + Midazolam 5 mg (Post-Baseline) N=24 nS (%) nE	All treatments N=24 nS (%) nE
Any AE	1 (4.2) 1	16 (66.7) 47	16 (66.7) 48

AEs of mild intensity	1 (4.2) 1	12 (50.0) 33	12 (50.0) 34
AEs of moderate intensity	0	7 (29.2) 12	7 (29.2) 12
AEs of severe intensity	0	2 (8.3) 2	2 (8.3) 2
Study drug-related AEs	0	4 (16.7) 5	4 (16.7) 5
Serious AEs	0	1 (4.2) 1	1 (4.2) 1
AEs leading to discontinuation of Study treament	0	1 (4.2) 1	1 (4.2) 1
Study-drug related AEs leading to discontinuation of study treatment	0	0	0
AEs leading to interruption of study treatment	0	1 (4.2) 1	1 (4.2) 1

N = number of subjects studied

nE = number of AE events in the category

nS = number of subjects with at least one AE in the category

% is based on the number of subjects

Conclusion:

This study demonstrated that the therapeutic dosing regimen of secukinumab did not change plasma exposure of concomitantly administered midazolam. More specifically, no “normalization” of CYP3A4 activity to a level similar to that in healthy persons with otherwise decreasing exposure to drugs metabolized by CYP3A4 was observed. This observation has clinical relevance for psoriasis patients who take drugs metabolized by CYP3A4 and that have a narrow therapeutic range. For those patients treated with secukinumab and concomitant CYP3A4-substrates, monitoring of these co-medications with potential dose adjustments is not needed.

Date of Clinical Trial Report

23 Aug 2017