Sponsor

Novartis Pharmaceuticals

Generic Drug Name

CJM112

Trial Indication(s)

Chronic plaque-type psoriasis

Protocol Number

CCJM112X2101

Protocol Title

A randomized, double-blind, placebo and positive controlled, single and multiple dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of CJM112 in chronic plaque-type psoriasis patients

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

Study Start/End Dates

Study Start Date: June 2013 (Actual)
Study Completion Date: October 2015 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a two-part, double-blind, randomized, placebo and positive controlled exploratory study of subcutaneous administration of CJM112 in chronic plaque-type psoriasis patients. The study was planned to be conducted in multiple centers with competitive enrollment in both study parts. Part I evaluated sequential single ascending doses (SAD) of sc CJM112 with placebo as control for each dose group and Part II evaluated multiple parallel dose groups (MD) of sc (subcutaneous) CJM112 with secukinumab as active control versus placebo over a treatment period of 12 weeks.

Centers

United States(18)

Publication

NCT01828086

Objectives:

Primary objectives

Part 1: To evaluate the safety and tolerability of ascending single sc doses of CJM112 in chronic plaque-type psoriasis patients.

Part 2: To evaluate the safety and tolerability of multiple sc doses of CJM112 in chronic plaque-type psoriasis patients.

Secondary objectives

Part 1:

- To assess the efficacy of ascending single sc doses of CJM112 in chronic plaque-type psoriasis patients, from baseline to Week 4.
- To assess the pharmacokinetics of CJM112 after single sc dosing.
- To assess the immunogenicity profile of CJM112 after single sc dosing.

Part 2:

- To assess the efficacy and dose-response of multiple sc doses of CJM112 compared with secukinumab sc and placebo in chronic
- plaque-type psoriasis patients, at Week 12.
- To assess the pharmacokinetics of CJM112 after multiple sc dosing.
- To assess the immunogenicity profile of CJM112 after multiple sc dosing.
- To explore the quality of life changes during the study, reported by the patient in a Dermatology Life Quality Index (DLQI).

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

In Part I a single subcutaneous injection of 5, 15, 50, 150 or 450mg CJM112 or placebo (mixture of inactive excipients matching the composition of CJM112 50mg) was administered.

In Part II, multiple subcutaneous injections of 15, 50, or 150mg (in two different dosing frequencies) CJM112; 150mg AIN457 (active comparator (AC)) or placebo were administered.

CJM112 15, 50 and 150mg (low frequency) dosing was weekly dosing alternating between active (A) and placebo (P) for 5 weeks, followed by alternate 2 weekly dosing for 4 weeks (ie W0:A, W1:P, W2:A, W3:P, W4:A followed by W6:P, W8:A, W10:P, W12:A)

CJM112 150mg high frequency dosing was a total of 9 doses; the first 5 at weekly intervals and the remaining 4 doses at 2 weekly intervals.

AIN457 dosing was weekly for 5 weeks, followed by alternating with placebo at 2 weekly intervals for 4 weeks (ie W0:AC, W1:AC, W2:AC, W3:AC, W4:AC followed by W6:P, W8:AC, W10:P, W12:AC)

Placebo was a total of 9 doses; the first 5 at weekly intervals and the remaining 4 doses at 2 weekly intervals. Some active treatment groups also received temporary placebo doses to match the application.

Statistical Methods

The analysis of the primary variable was to establish a maximum tolerated dose (MTD). The MTD was determined as being the highest dose for which no related SAE occurred. The number of treatment related SAE's was tabulated and the determination of MTD was presented separately for each study part.

For Part I of the study, efficacy in psoriasis patients was analyzed through a Bayesian analysis of the change from baseline in PASI score 4 weeks after treatment to compare CJM112 treatment groups vs the Placebo treatment group. Dose group was treated as a factor in the model and baseline PASI score was included as a covariate.

For Part II of the study, efficacy was measured by the number of responders after 12 weeks of treatment. The number of responders was compared using a Bayesian analysis with dose group as a factor to compare CJM112 against Secukinumab and Placebo.

Three interim analyses (IA) were done in the Part I. Forth IA was done once most patients had completed Part I of the study to confirm dose selections chosen for Part II. The final interim analysis for Part I of the study was conducted once the database had locked. Two further interim analyses were conducted for Part II of the study

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Men or women 18-65 years of age at time of consent
• Chronic plaque-type psoriasis diagnosed for at least 6 months at time of randomization
• At randomization, moderate to severe psoriasis as defined by:
• PASI score of 12 or greater and,
• IGA score of 3 or greater and,
• Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater.
• Female patients may be included according to the following:
Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, using highly effective methods of contraception during dosing and for 5 times the terminal half-life of study treatment.
• Male subjects must agree to comply with two highly effective contraceptive methods

Exclusion Criteria:
• Forms of psoriasis other than chronic plaque-type (incl. drug induced psoriasis)
• Ongoing use of prohibited psoriasis treatments and other prohibited medication at randomization. Washout periods detailed in the protocol have to be adhered to
• Previous treatment with IL-17 or IL17R blocking agents, including secukinumab
• Any live vaccines (including nasal-spray flu vaccine) starting from 6 weeks before screening, during the study, and up to 24 weeks after the last dose of CJM112 or secukinumab
• Evidence of active tuberculosis at screening

• Active systemic infections (other than common cold)
• Pregnant or nursing (lactating) women

Participant Flow Table

Part I Patient disposition - n (percent) of patients (Part I – SAD)

	CJM112 5 mg SAD N=4 n (%)	CJM112 15 mg SAD N=4 n (%)	CJM112 50 mg SAD N=12 n (%)	CJM112 150 mg SAD N=4 n (%)	CJM112 450 mg SAD N=4 n (%)	CJM112 Total SAD N=28 n (%)	Placebo SAD N=14 n (%)	Total N=42 n (%)
Patients								
Completed	3 (75.0)	4 (100.0)	11 (91.7)	4 (100.0)	4 (100.0)	26 (92.9)	14 (100.0)	40 (95.2)
Discontinued	1 (25.0)	0	1 (8.3)	0	0	2 (7.1)	0	2 (4.8)
Main cause of discontinuation								
Lost to follow-up	1 (25.0)	0	1 (8.3)	0	0	2 (7.1)	0	2 (4.8)

Part II Patient disposition - n (percent) of patients (Part II - MD)

	CJM112 150 mg High MD N=11 n (%)	CJM112 150 mg Low MD N=10 n (%)	CJM112 50 mg MD N=10 n (%)	CJM112 15 mg MD N=11 n (%)	CJM112 Total MD N=42 n (%)	Secukinumab 150 mg MD N=6 n (%)	Placebo MD N=6 n (%)	Total N=54 n (%)
Patients								
Randomized	11 (100.0)	10 (100.0)	10 (100.0)	11 (100.0)	42 (100.0)	6 (100.0)	6 (100.0)	54 (100.0)
Completed	8 (72.7)	9 (90.0)	9 (90.0)	11 (100.0)	37 (88.1)	6 (100.0)	6 (100.0)	49 (90.7)
Discontinued	3 (27.3)	1 (10.0)	1 (10.0)	0	5 (11.9)	0	0	5 (9.3)
Main cause of discontinuation								
Adverse events	2 (18.2)	0	0	0	2 (4.8)	0	0	2 (3.7)
Lost to follow-up	1 (9.1)	0	1 (10.0)	0	2 (4.8)	0	0	2 (3.7)
Protocol deviation	0	1 (10.0)	0	0	1 (2.4)	0	0	1 (1.9)

Baseline Characteristics

Part I Demographic summary by treatment group (Part I - SAD)

		CJM112 5 mg SAD N=4	CJM112 15 mg SAD N=4	CJM112 50 mg SAD N=12	CJM112 150 mg SAD N=4	CJM112 450 mg SAD N=4	CJM112 Total SAD N=28	Placebo SAD N=14	Total N=42
Age (years)	Mean (SD)	43.0 (10.55)	41.8 (7.80)	41.0 (11.04)	47.5 (18.72)	43.0 (13.44)	42.6 (11.52)	48.9 (7.08)	44.7 (10.59)
	Median	44.5	43.0	44.0	52.0	47.5	45.5	50.0	48.0
	Range	(30, 53)	(32, 49)	(20, 60)	(21, 65)	(24, 53)	(20, 65)	(35, 59)	(20, 65)
Sex - n (%)	Male	3 (75.0)	3 (75.0)	6 (50.0)	2 (50.0)	4 (100.0)	18 (64.3)	10 (71.4)	28 (66.7)
	Female	1 (25.0)	1 (25.0)	6 (50.0)	2 (50.0)	0	10 (35.7)	4 (28.6)	14 (33.3)
Race - n (%)	Caucasian	3 (75.0)	3 (75.0)	9 (75.0)	3 (75.0)	4 (100.0)	22 (78.6)	14 (100.0)	36 (85.7)
	Black	0	0	1 (8.3)	0	0	1 (3.6)	0	1 (2.4)
	Asian	1 (25.0)	0	1 (8.3)	1 (25.0)	0	3 (10.7)	0	3 (7.1)
	Other	0	1 (25.0)	1 (8.3)	0	0	2 (7.1)	0	2 (4.8)
Ethnicity - n (%)	Hispanic/Latino	0	2 (50.0)	4 (33.3)	2 (50.0)	1 (25.0)	9 (32.1)	6 (42.9)	15 (35.7)
	Mixed Ethnicity	1 (25.0)	0	0	0	0	1 (3.6)	0	1 (2.4)
	Other	3 (75.0)	2 (50.0)	8 (66.7)	2 (50.0)	3 (75.0)	18 (64.3)	8 (57.1)	26 (61.9)
Weight (kg)	Mean (SD)	95.80 (11.799)	98.75 (12.714)	113.71 (56.248)	75.60 (19.408)	90.05 (21.912)	100.19 (40.085)	97.47 (15.144)	99.28 (33.653)
	Median	92.55	98.95	109.85	72.45	82.25	89.70	94.60	93.85
	Range	(86.2, 111.9)	(87.1, 110.0)	(52.5, 275.0)	(55.5, 102.0)	(73.4, 122.3)	(52.5, 275.0)	(79.2, 134.2)	(52.5, 275.0)
BMI (kg/m^2)	Mean (SD)	33.324 (1.1687)	32.786 (5.6957)	39.750 (18.9119)	26.349 (4.3366)	27.950 (4.4381)	34.237 (13.5191)	32.118 (5.5249)	33.531 (11.4480)
	Median	33.305	32.121	37.353	26.762	26.498	32.372	31.925	32.153
	Range	(32.05, 34.64)	(26.98, 39.92)	(18.38, 92.20)	(21.41, 30.46)	(24.38, 34.42)	(18.38, 92.20)	(24.18, 41.14)	(18.38, 92.20)

Summary of psoriasis medical history by treatment group (Part I-SAD)

		CJM112 5 mg SAD N=4	CJM112 15 mg SAD N=4	CJM112 50 mg SAD N=12	CJM112 150 mg SAD N=4	CJM112 450 mg SAD N=4	CJM112 Total SAD N=28	Placebo SAD N=14	Total N=42
Baseline PASI	Mean (SD)	17.23 (8.757)	17.13 (6.203)	18.20 (4.309)	23.13 (9.716)	14.23 (1.269)	18.04 (6.103)	21.91 (9.668)	19.33 (7.587)
	Median	13.30	15.40	15.90	21.35	13.70	15.45	20.05	16.15
	Range	(12.0, 30.3)	(12.0, 25.7)	(14.8, 27.6)	(13.4, 36.4)	(13.4, 16.1)	(12.0, 36.4)	(12.3, 48.6)	(12.0, 48.6)
Baseline DLQI	Mean (SD)	11.00 (5.354)	10.75 (8.958)	12.17 (8.376)	14.00 (7.616)	8.75 (4.856)	11.57 (7.218)	13.57 (8.751)	12.24 (7.714)
	Median	11.50	10.50	12.00	11.50	8.00	10.50	11.00	10.50
	Range	(4.0, 17.0)	(1.0, 21.0)	(0.0, 23.0)	(8.0, 25.0)	(4.0, 15.0)	(0.0, 25.0)	(3.0, 30.0)	(0.0, 30.0)
Psoriasis:									
Time since diagnosis (years)	Mean (SD)	5.33 (3.717)	17.51 (15.428)	14.58 (8.261)	11.65 (10.653)	10.81 (2.501)	12.31 (8.639)	15.45 (12.284)	13.33 (9.884)
	Median	4.33	19.63	11.35	5.99	10.54	10.04	12.32	10.80
	Range	(2.1, 10.6)	(1.1, 31.8)	(7.6, 30.3)	(5.0, 23.9)	(8.1, 14.1)	(1.1, 31.8)	(2.6, 42.3)	(1.1, 42.3)
Psoriasis arthritis:									
History - n (%)	Yes	1 (25.0)	1 (25.0)	1 (8.3)	0	0	3 (10.7)	3 (21.4)	6 (14.3)
	No	3 (75.0)	3 (75.0)	11 (91.7)	4 (100.0)	4 (100.0)	25 (89.3)	11 (78.6)	36 (85.7)
Time since diagnosis (years)	Mean (SD)	10.56	13.63	7.79	NA*	NA*	10.66 (2.920)	4.95 (4.143)	8.38 (4.284)
	Median	10.56	13.63	7.79			10.56	4.95	7.88
	Range	(10.6, 10.6)	(13.6, 13.6)	(7.8, 7.8)			(7.8, 13.6)	(2.0, 7.9)	(2.0, 13.6)

If the date of diagnosis is partial, the date was imputed as 1st of the month (if day was missing) or as 1st of January (if day and month were missing).
NA*: Not available, it elaborates the fact that in these groups no patient had history of PsA thus time since diagnosis for this is not available

Part II Demographic summary by treatment group (Part II - MD)

		CJM112 150 mg High MD N=11	CJM112 150 mg Low MD N=10	CJM112 50 mg MD N=10	CJM112 15 mg MD N=11	CJM112 Total MD N=42	Secukinumab 150 mg MD N=6	Placebo MD N=6	Total N=54
Age (years)	Mean (SD)	44.3 (11.79)	44.4 (8.03)	41.5 (9.63)	45.3 (9.79)	43.9 (9.68)	51.7 (6.41)	41.7 (14.69)	44.5 (10.19)
	Median	47.0	41.5	43.5	46.0	44.0	52.0	40.5	44.0
	Range	(22, 56)	(35, 59)	(26, 53)	(30, 65)	(22, 65)	(44, 59)	(25, 60)	(22, 65)
Sex - n (%)	Male	7 (63.6)	7 (70.0)	7 (70.0)	9 (81.8)	30 (71.4)	3 (50.0)	2 (33.3)	35 (64.8)
	Female	4 (36.4)	3 (30.0)	3 (30.0)	2 (18.2)	12 (28.6)	3 (50.0)	4 (66.7)	19 (35.2)
Race - n (%)	Caucasian	10 (90.9)	9 (90.0)	8 (80.0)	9 (81.8)	36 (85.7)	6 (100.0)	6 (100.0)	48 (88.9)
	Black	1 (9.1)	1 (10.0)	1 (10.0)	1 (9.1)	4 (9.5)	0	0	4 (7.4)
	Asian	0	0	0	1 (9.1)	1 (2.4)	0	0	1 (1.9)
	Other	0	0	1 (10.0)	0	1 (2.4)	0	0	1 (1.9)
Ethnicity - n (%)	Hispanic/Latino	4 (36.4)	4 (40.0)	6 (60.0)	5 (45.5)	19 (45.2)	4 (66.7)	2 (33.3)	25 (46.3)
	Chinese	0	0	0	1 (9.1)	1 (2.4)	0	0	1 (1.9)
	Mixed Ethnicity	0	0	1 (10.0)	0	1 (2.4)	0	0	1 (1.9)
	Other	7 (63.6)	6 (60.0)	3 (30.0)	5 (45.5)	21 (50.0)	2 (33.3)	4 (66.7)	27 (50.0)
Weight (kg)	Mean (SD)	105.66 (29.116)	93.75 (13.973)	111.56 (33.817)	102.95 (33.220)	103.52 (28.464)	90.63 (13.760)	74.53 (20.150)	98.87 (27.835)
	Median	98.10	96.55	94.90	90.90	95.85	88.30	68.10	92.20
	Range	(63.0, 162.9)	(69.0, 116.4)	(78.6, 171.3)	(68.7, 180.5)	(63.0, 180.5)	(76.5, 116.3)	(51.0, 101.7)	(51.0, 180.5)
BMI (kg/m^2)	Mean (SD)	36.271 (8.4140)	30.686 (6.1681)	37.010 (9.6352)	35.931 (12.1663)	35.028 (9.3963)	33.465 (5.8057)	26.868 (4.9738)	33.948 (8.9688)
	Median	33.160	29.604	37.071	29.580	32.399	32.930	26.470	31.661
	Range	(25.56, 52.27)	(24.28, 43.42)	(23.04, 51.54)	(25.80, 60.31)	(23.04, 60.31)	(24.98, 42.54)	(19.29, 33.38)	(19.29, 60.31)

	CJM112 150 mg High MD N=11	CJM112 150 mg Low MD N=10	CJM112 50 mg MD N=10	CJM112 15 mg MD N=11	CJM112 Total MD N=42	Secukinumab 150 mg MD N=6	Placebo MD N=6	Total N=54

Summary of psoriasis medical history by treatment group (Part II-MD)

		CJM112 150 mg High MD N=11	CJM112 150 mg Low MD N=10	CJM112 50 mg MD N=10	CJM112 15 mg MD N=11	CJM112 Total MD N=42	Secukinumab 150 mg MD N=6	Placebo MD N=6	Total N=54
Baseline PASI	Mean (SD)	18.42 (5.067)	21.92 (8.720)	18.43 (9.672)	24.84 (12.416)	20.94 (9.415)	17.50 (6.058)	22.80 (9.383)	20.76 (9.057)
	Median	16.50	21.00	16.20	21.90	17.00	15.35	22.10	16.70
	Range	(14.2, 32.3)	(12.6, 40.0)	(12.6, 45.6)	(12.0, 54.0)	(12.0, 54.0)	(13.8, 29.8)	(12.9, 34.8)	(12.0, 54.0)
Baseline DLQI	Mean (SD)	12.64 (5.482)	16.20 (6.286)	11.90 (5.195)	16.73 (8.545)	14.38 (6.659)	14.00 (7.746)	14.00 (4.980)	14.30 (6.506)
	Median	11.00	13.50	12.50	18.00	12.50	11.50	12.50	12.50
	Range	(4.0, 26.0)	(11.0, 29.0)	(1.0, 19.0)	(2.0, 28.0)	(1.0, 29.0)	(6.0, 27.0)	(9.0, 21.0)	(1.0, 29.0)
Psoriasis:									
Time since diagnosis (years)	Mean (SD)	21.76 (13.708)	13.52 (7.357)	12.21 (7.581)	14.64 (13.054)	15.66 (11.232)	9.65 (5.361)	16.85 (13.291)	15.13 (10.997)
	Median	20.20	15.00	10.28	6.92	16.45	7.42	12.70	13.00
	Range	(4.1, 50.8)	(3.5, 22.2)	(0.7, 24.5)	(1.1, 37.7)	(0.7, 50.8)	(5.2, 19.0)	(3.6, 38.2)	(0.7, 50.8)
Psoriasis arthritis:									
History - n (%)	Yes	3 (27.3)	3 (30.0)	2 (20.0)	4 (36.4)	12 (28.6)	2 (33.3)	1 (16.7)	15 (27.8)
	No	8 (72.7)	7 (70.0)	8 (80.0)	7 (63.6)	30 (71.4)	4 (66.7)	5 (83.3)	39 (72.2)
Time since diagnosis (years)	Mean (SD)	28.97 (30.882)	10.24 (8.454)	6.45 (4.838)	3.92 (3.085)	10.66 (14.271)	7.06 (0.052)	NA	10.11 (13.098)
	Median	28.97	12.92	6.45	4.35	6.94	7.06		7.02
	Range	(7.1, 50.8)	(0.8, 17.0)	(3.0, 9.9)	(0.1, 6.9)	(0.1, 50.8)	(7.0, 7.1)		(0.1, 50.8)

NA: not available
Note: Patients #1023/5314 (CJM112 150 mg High) and #1023/5347 (Placebo) were not diagnosed with psoriasis arthritis by a physician and therefore the time since diagnosis is unknown

Summary of Efficacy

Primary Outcome Result(s)

There was no maximal tolerated dose up to a single dose of 450 mg CJM112 defined by pre-set criteria.

Refer to safety result section for primary outcome result.

Secondary Outcome Result(s)

Part I – Summary of absolute PASI change from baseline scores at Week 4 after single dose

PASI scores (change from baseline)	CJM112 5 mg SAD N=4	CJM112 15 mg SAD N=4	CJM112 50 mg SAD N=12	CJM112 150 mg SAD N=4	CJM112 450 mg SAD N=4	Placebo SAD N=14
Mean (SD)	0.00 (0.000)	-5.35 (2.517)	-10.33 (7.346)	-17.15 (4.728)	-8.83 (3.639)	-3.91 (7.171)
Median	0.00	-5.15	-6.40	-16.75	-9.85	-3.05
Range	(0.0, 0.0)	(-8.0, -3.1)	(-20.4, 1.7)	(-23.1, -12.0)	(-12.0, -3.6)	(-21.3, 12.5)

Part II - Summary of PASI response rates at 12 weeks

	CJM112 150 mg High MD N=11 n (%)	CJM112 150 mg Low MD N=10 n (%)	CJM112 50 mg MD N=10 n (%)	CJM112 15 mg MD N=11 n (%)	Secukinumab 150 mg MD N=6 n (%)	Placebo MD N=6 n (%)	Total N=54 n (%)
PASI75	7 (63.6)	9 (90.0)	4 (40.0)	3 (27.3)	4 (66.7)	0	27 (50.0)

	CJM112 150 mg High MD N=11 n (%)	CJM112 150 mg Low MD N=10 n (%)	CJM112 50 mg MD N=10 n (%)	CJM112 15 mg MD N=11 n (%)	Secukinumab 150 mg MD N=6 n (%)	Placebo MD N=6 n (%)	Total N=54 n (%)
PASI90	4 (36.4)	6 (60.0)	3 (30.0)	1 (9.1)	2 (33.3)	0	16 (29.6)
PASI100	1 (9.1)	3 (30.0)	3 (30.0)	0	1 (16.7)	0	8 (14.8)

Part I: Summary statistics of total CJM112 serum PK parameters by treatment group

Summary statistics of total CJM112 serum PK parameters by treatment group (Part I - SAD)

Treatment	Statistic	AUCinf / dose[a]	AUCinf[b]	CL/F[c]	Cmax[d]	Cmax / dose[e]	T1/2[f]	Tmax[g]	Vz/F[h]
5 mg	n				1	1		1	
	Mean (SD)	n.c.	n.c.	n.c.	0.343	0.0686	n.c.	n.c.	n.c.
	CV% mean	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
	Median				0.343	0.0686		3.00	
	Range	n.c.	n.c.	n.c.	(0.343, 0.343)	(0.0686, 0.0686)	n.c.	(3.00, 3.00)	n.c.
15 mg	n	2	2	2	4	4	2	4	2
	Mean (SD)	2.27 (1.63)	34.0 (24.4)	0.593 (0.425)	0.625 (0.391)	0.0417 (0.0261)	17.4 (6.89)		12.7 (4.76)
	CV% mean	71.7	71.7	71.7	62.5	62.5	39.7		37.3
	Median	2.27	34.0	0.593	0.536	0.0357	17.4	6.98	12.7
	Range	(1.12, 3.42)	(16.8, 51.3)	(0.293, 0.894)	(0.260, 1.17)	(0.0173, 0.0780)	(12.5, 22.2)	(6.96, 7.02)	(9.38, 16.1)
50 mg	n	8	8	8	12	12	8	12	8
	Mean (SD)	2.56 (1.13)	128 (56.7)	0.478 (0.257)	2.74 (1.50)	0.0548 (0.0300)	18.8 (8.79)		10.8 (1.98)
	CV% mean	44.2	44.2	53.6	54.6	54.6	46.7		18.3
	Median	2.52	126	0.409	3.31	0.0661	16.9	6.50	10.9
	Range	(0.981, 4.59)	(49.0, 230)	(0.218, 1.02)	(0.248, 4.59)	(0.00496, 0.0918)	(9.21, 36.1)	(1.96, 14.0)	(8.14, 13.6)
150 mg	n	4	4	4	4	4	4	4	4

Treatment	Statistic	AUCinf / dose[a]	AUCinf[b]	CL/F[c]	Cmax[d]	Cmax / dose[e]	T1/2[f]	Tmax[g]	Vz/F[h]	
	Mean (SD)	2.27 (0.441)	341 (66.1)	0.455 (0.107)	10.2 (2.73)	0.0678 (0.0182)	19.1 (2.28)			12.5 (3.45)
	CV% mean	19.4	19.4	23.4	26.8	26.8	12.0			27.5
	Median	2.42	363	0.413	10.9	0.0729	19.1	4.98		11.5
	Range	(1.63, 2.63)	(245, 394)	(0.381, 0.613)	(6.51, 12.3)	(0.0434, 0.0820)	(16.3, 21.7)	(3.00, 7.10)		(9.60, 17.5)
450 mg	n	4	4	4	4	4	4	4		4
	Mean (SD)	3.95 (1.38)	1780 (623)	0.278 (0.0967)	37.2 (5.14)	0.0827 (0.0114)	29.6 (12.8)			10.6 (1.43)
	CV% mean	35.0	35.0	34.7	13.8	13.8	43.3			13.5
	Median	3.86	1740	0.280	37.5	0.0832	28.8	7.09		10.9
	Range	(2.72, 5.36)	(1220, 2410)	(0.186, 0.368)	(31.7, 42.2)	(0.0704, 0.0938)	(16.3, 44.5)	(3.00, 14.0)		(8.67, 12.0)

CV% = Coefficient of variation (%) = sd/mean*100:

CV% geo mean = sqrt(exp(variance for log transformed data)-1)) * 100.

Geo-mean, CV (%) and CV(%) geo-mean are presented only if data does not include zero.

Parameter units: [a] AUCinf/dose in day*µg/mL/mg, [b] AUCinf in day*µg/mL, [c] CL/F in L/day, [d] Cmax in µg/mL, [e] Cmax/dose in µg/mL/mg, [f] T1/2 in day, [g] Tmax in day, [h] Vz/F in L

n.c. : not calculated because of insufficient data

Summary statistics of total CJM112 serum concentration at end of treatment period (Ctrough at close to steady state conditions) and at end of study visit by treatment group (Part II - MD)

Visit DAY	Scheduled timepoint (hr)	n	Mean (SD) (µg/mL)	CV% Mean [d]	Geo-mean (µg/mL)	CV% geo-mean [e]	Median (µg/mL)	[Min;Max] (µg/mL)
CJM112 150 mg High MD								
DAY57	0	9	17.6 (10.4)	59.2	14.6	78.5	19.3	[4.71;34.6]
DAY71[a]	0	9	21.2 (19.1)	90.5	15.9	92.6	17.6	[5.21;67.7]
DAY85[b]	0	9	18.4 (13.1)	71.3	14.7	82.3	15.6	[5.21;47.0]
EOS	1344	10	5.03 (4.20)	83.4	3.18	166.1	4.61	[0.677;10.9]
CJM112 150 mg Low MD								
DAY57[a]	0	10	6.41 (4.37)	68.2	-	-	6.15	[0.000;14.7]
DAY85[b]	0	8	7.14 (4.37)	61.2	5.94	77.5	5.38	[1.68;14.4]
DAY113	672	9	7.01 (4.05)	57.7	5.79	83.0	6.70	[1.31;14.7]
EOS	1344	9	2.73 (2.09)	76.6	2.08	100.7	2.35	[0.461;7.49]
CJM112 50 mg MD								
DAY57[a]	0	9	2.47 (1.34)	54.0	2.14	63.9	2.42	[0.918;4.25]
DAY85[b]	0	9	2.14 (1.36)	63.7	1.81	66.3	1.76	[0.796;4.68]
DAY113	672	9	1.77 (0.965)	54.6	1.56	56.6	1.45	[0.758;3.35]
EOS	1344	9	0.623 (0.540)	86.7			0.525	[0.000;1.54]
CJM112 15 mg MD								
DAY57[a]	0	10	0.963 (0.409)	42.5	0.870	54.1	0.915	[0.354;1.66]
DAY85[b]	0	11	0.782 (0.390)	49.9	-	-	0.890	[0.000;1.32]
DAY113	672	11	0.742 (0.435)	58.6	-	-	0.667	[0.000;1.46]
EOS	1344	11	0.121 (0.212)	175.3	-	-	0.000	[0.000;0.503]
Secukinumab 150 mg MD								
DAY57[a]	0	6	31.1 (10.9)	35.1	29.6	34.8	26.5	[19.8;46.4]
DAY85[b]	0	6	20.1 (11.2)	55.5	18.2	49.0	17.1	[10.4;42.0]
DAY113	672	6	16.8 (9.22)	55.0	15.4	43.5	13.4	[11.5;35.5]
EOS	1344	6	8.22 (5.63)	68.5	7.05	62.0	5.91	[3.84;19.0]

[a] Penultimate dose, [b] Last dose, [c] pre-dose sample

[d] CV(%)=SD/mean * 100, [e] CV(%) geometric mean = sqrt(exp(variance for log transformed data)-1)*100.

All concentrations below the lower limit of quantification were treated as zero.

Part I - Summary of DLQI change from baseline score at Week 4 (Part I - SAD)

DLQI scores (change from baseline)	CJM112 5 mg SAD N=4	CJM112 15 mg SAD N=4	CJM112 50 mg SAD N=12	CJM112 150 mg SAD N=4	CJM112 450 mg SAD N=4	Placebo SAD N=14
Mean (SD)	-1.0 (1.73)	-5.0 (4.24)	-7.3 (6.68)	-9.5 (4.20)	-7.0 (2.94)	-3.4 (5.39)
Median	-2.0	-5.5	-6.0	-9.0	-7.0	-1.0
Range	(-2, 1)	(-9, 0)	(-18, 0)	(-15, -5)	(-10, -4)	(-15, 2)

Part II - Summary of DLQI change from baseline score at Week 12 (Part II-MD)

DLQI scores (change from baseline)	CJM112 150 mg High MD N=11	CJM112 150 mg Low MD N=10	CJM112 50 mg MD N=10	CJM112 15 mg MD N=11	Secukinumab 150 mg MD N=6	Placebo MD N=6
Mean (SD)	-10.9 (5.80)	-13.7 (6.11)	-8.0 (5.77)	-8.5 (10.09)	-10.8 (4.88)	-1.2 (8.06)
Median	-11.0	-12.0	-9.0	-7.0	-10.5	-2.0
Range	(-22, -2)	(-24, -5)	(-15, -1)	(-27, 5)	(-19, -4)	(-10, 12)

Part I –SAD Immunogenicity

Part I - Summary of treatment-induced or boosted ADA (anti-drug antibodies) per group at any time (Part I - SAD)

ADA antibodies	CJM112 5 mg SAD N=4	CJM112 15 mg SAD N=4	CJM112 50 mg SAD N=12	CJM112 150 mg SAD N=4	CJM112 450 mg SAD N=4	Placebo SAD N=14
Yes (%)	0 (0)	0 (0)	1 (8)	2 (50)	1 (25)	0 (0)
No (%)	4 (100)	4 (100)	11 (92)	2 (50)	3 (75)	14 (100)

Part II –MAD Immunogenicity

Anti-secukinumab antibodies : none of the patients had anti-secukinumab antibodies.

Part II - Summary of treatment-induced or boosted ADA (anti-drug antibodies) per group at any time (Part II - MAD)

DLQI scores (change from baseline)	CJM112 150 mg High MD N=11	CJM112 150 mg Low MD N=10	CJM112 50 mg MD N=10	CJM112 15 mg MD N=11	Secukinumab 150 mg MD N=6	Placebo MD N=6
Yes (%)	0 (0)	1 (10)	0 (0)	5 (46)	0 (0)	0 (0)
No (%)	11 (100)	9 (90)	10 (100)	6 (54)	6 (100)	6 (100)

Summary of Safety

Safety Results

Incidence of AEs by primary system organ class (Safety set) (Part I)

	CJM112 5 mg N=4 n (%)	CJM112 15 mg N=4 n (%)	CJM112 50 mg N=12 n (%)	CJM112 150 mg N=4 n (%)	CJM112 450 mg N=4 n (%)	CJM112 Total N=28 n (%)	Placebo N=14 n (%)	Total N=42 n (%)
Patients with AEs	1 (25.0)	2 (50.0)	5 (41.7)	2 (50.0)	3 (75.0)	13 (46.4)	8 (57.1)	21 (50.0)
System organ class								
Infections and infestations	0	1 (25.0)	3 (25.0)	0	2 (50.0)	6 (21.4)	1 (7.1)	7 (16.7)
Skin and subcutaneous tissue disorders	0	0	0	1 (25.0)	1 (25.0)	2 (7.1)	3 (21.4)	5 (11.9)
Gastrointestinal disorders	0	0	1 (8.3)	1 (25.0)	1 (25.0)	3 (10.7)	1 (7.1)	4 (9.5)
Nervous system disorders	0	1 (25.0)	2 (16.7)	0	1 (25.0)	4 (14.3)	0	4 (9.5)
General disorders and administration site conditions	0	0	1 (8.3)	1 (25.0)	0	2 (7.1)	1 (7.1)	3 (7.1)
Investigations	0	0	1 (8.3)	0	1 (25.0)	2 (7.1)	1 (7.1)	3 (7.1)
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (25.0)	1 (3.6)	2 (14.3)	3 (7.1)
Respiratory, thoracic and mediastinal disorders	1 (25.0)	1 (25.0)	0	0	0	2 (7.1)	1 (7.1)	3 (7.1)

	CJM112 5 mg N=4 n (%)	CJM112 15 mg N=4 n (%)	CJM112 50 mg N=12 n (%)	CJM112 150 mg N=4 n (%)	CJM112 450 mg N=4 n (%)	CJM112 Total N=28 n (%)	Placebo N=14 n (%)	Total N=42 n (%)
Injury, poisoning and procedural complications	0	0	0	0	1 (25.0)	1 (3.6)	1 (7.1)	2 (4.8)
Psychiatric disorders	0	0	0	1 (25.0)	0	1 (3.6)	1 (7.1)	2 (4.8)
Blood and lymphatic system disorders	0	0	0	0	0	0	1 (7.1)	1 (2.4)
Cardiac disorders	0	0	0	0	0	0	1 (7.1)	1 (2.4)
Immune system disorders	0	0	0	1 (25.0)	0	1 (3.6)	0	1 (2.4)
Metabolism and nutrition disorders	0	0	0	1 (25.0)	0	1 (3.6)	0	1 (2.4)
Reproductive system and breast disorders	0	0	0	0	0	0	1 (7.1)	1 (2.4)
Vascular disorders	0	0	0	1 (25.0)	0	1 (3.6)	0	1 (2.4)

Arranged in descending order of frequency (in total group).

Incidence of AEs by primary system organ class - n(percent) of patients (Part II - MD)

	CJM112 150 mg High MD N=11 n (%)	CJM112 150 mg Low MD N=10 n (%)	CJM112 50 mg MD N=10 n (%)	CJM112 15 mg MD N=11 n (%)	CJM112 Total MD N=42 n (%)	Secukinumab 150 mg MD N=6 n (%)	Placebo MD N=6 n (%)	Total N=54 n (%)
Patients with AE(s)	9 (81.8)	4 (40.0)	5 (50.0)	5 (45.5)	23 (54.8)	2 (33.3)	5 (83.3)	30 (55.6)
System organ class								
Infections and infestations	6 (54.5)	2 (20.0)	1 (10.0)	0	9 (21.4)	1 (16.7)	2 (33.3)	12 (22.2)
Skin and subcutaneous tissue disorders	1 (9.1)	3 (30.0)	1 (10.0)	2 (18.2)	7 (16.7)	0	1 (16.7)	8 (14.8)
Gastrointestinal disorders	1 (9.1)	1 (10.0)	2 (20.0)	1 (9.1)	5 (11.9)	1 (16.7)	0	6 (11.1)
Nervous system disorders	0	1 (10.0)	2 (20.0)	2 (18.2)	5 (11.9)	0	1 (16.7)	6 (11.1)
Investigations	0	2 (20.0)	2 (20.0)	0	4 (9.5)	0	1 (16.7)	5 (9.3)
Musculoskeletal and connective tissue disorders	1 (9.1)	1 (10.0)	1 (10.0)	1 (9.1)	4 (9.5)	0	1 (16.7)	5 (9.3)
Injury, poisoning and procedural complications	3 (27.3)	1 (10.0)	0	0	4 (9.5)	0	0	4 (7.4)
Respiratory, thoracic and mediastinal disorders	1 (9.1)	1 (10.0)	0	0	2 (4.8)	0	1 (16.7)	3 (5.6)
Cardiac disorders	1 (9.1)	0	1 (10.0)	0	2 (4.8)	0	0	2 (3.7)
General disorders and administration site conditions	1 (9.1)	0	0	1 (9.1)	2 (4.8)	0	0	2 (3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (10.0)	0	1 (9.1)	2 (4.8)	0	0	2 (3.7)

	CJM112 150 mg High MD N=11 n (%)	CJM112 150 mg Low MD N=10 n (%)	CJM112 50 mg MD N=10 n (%)	CJM112 15 mg MD N=11 n (%)	CJM112 Total MD N=42 n (%)	Secukinumab 150 mg MD N=6 n (%)	Placebo MD N=6 n (%)	Total N=54 n (%)
Psychiatric disorders	0	0	1 (10.0)	0	1 (2.4)	0	1 (16.7)	2 (3.7)
Eye disorders	0	0	0	1 (9.1)	1 (2.4)	0	0	1 (1.9)
Immune system disorders	0	0	1 (10.0)	0	1 (2.4)	0	0	1 (1.9)
Metabolism and nutrition disorders	0	1 (10.0)	0	0	1 (2.4)	0	0	1 (1.9)
Renal and urinary disorders	1 (9.1)	0	0	0	1 (2.4)	0	0	1 (1.9)
Reproductive system and breast disorders	0	0	0	1 (9.1)	1 (2.4)	0	0	1 (1.9)

Arranged in descending order of frequency (in total group).

Serious Adverse Events by System Organ Class

	CJM112 5mg s.c. SAD N = 4	CJM112 15mg s.c. SAD N = 4	CJM112 50mg s.c. SAD N = 12	CJM112 150mg s.c. SAD N = 4	CJM112 450mg s.c. SAD N = 4	Placebo SAD N = 14	CJM112 150mg s.c. high frequency dosing MD N = 11	CJM112 150mg s.c. low frequency dosing MD N = 10	CJM112 50mg s.c. MD N = 10	CJM112 15mg s.c. MD N = 11	Secukinumab 150mg s.c. MD N = 6	Placebo MD N = 6
Total participants affected	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (25.00 %)	0 (0.00 %)	1 (7.14 %)	1 (9.09 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00 %)
Injury, poisoning and procedural complications												
Postoperative respiratory failure[1, †]	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (9.09 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00 %)
Musculoskeletal and connective tissue disorders												
Back pain[1, †]	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (7.14 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00 %)
Renal and urinary disorders												

Acute kidney injury[1, †]	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (9.09 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00 %)
Vascular disorders												
Hypertensive crisis[1, †]	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (25.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00 %)

† Systematic Assessment: 1 MedDRA

Other Relevant Findings

Not Applicable

Conclusion:

This is the first-in-human study of CJM112 a high-affinity monoclonaöl antibody directed against human IL-17A. It was conducted in patients with plaque Psortiasis in two parts: a placebo-controlled single ascending dose Part preceeding a second randomized placebo- and active-controlled multiple dose Part. In the single-dose part, doses within a 90-fold range (between 5 and 450 mg per body) were tested. In the multiple dose part, individual doses between 15 and 150 mg given in different intervals over a 12-week period were tested.

Efficacy – In the single-ascending dose Part of the study, the mean psoriasis area and severity index (PASI) time profiles are better than placebo for the 15 mg (second lowest) and all higher dose groups, indicating a clinical effect on psoriasis. This effect started in the first weeks and was sustained over at least three months in the highest dose group (450 mg). The results from the single dose cohort 50 mg met the pre-defined promising efficacy criterion,. Efficacy results appear best in the 150 mg dose group with 2 out of 4 patients reaching PASI90 at Day 29, however, this group may be skewed to positive response by lower body weight and higher baseline PASI scores. The 450 mg dose group did not significantly add any further efficacy benefit but seemed to prolong the efficacy duration. Thus, a single dose of 150 mg may have achieved already a ceiling effect in terms of maximal efficacy.

In the multiple dose group, CJM112 showed clinical activity in all dose groups tested (between 15 and 150 mg with different dosing intervals), both in terms of PD-markers (reduction of beta-defensin-2) as well as for clinical signs. In contrast to the placebo group, all active treatment groups for CJM112 and secukinumab had clinical responders (PASI50) at Day 85. The most efficacious dose group was CJM 150 Low (150 mg q4 weeks with a single additional loading after 2 weeks).

All three higher CJM112 dose groups appear to have a similar efficacy as the secukinumab active control group and similar to secukinumab historical groups, hinting to a “ceiling effect” for anti-IL-17A therapy in Psoriasis.

Safety - In the single-ascending dose portion of the study, no significant safety signals have been detected. Although difficult to conclude given the low number of patients, the overall AE frequency in the CJM112-dosed patients is similar to placebo and there was no specific AE or class of individual AEs that occurred in a relevant higher frequency, including infections. However, there were more AEs classified as “related” in the CJM112 450 mg group than in the other treatment groups, but all of those were experienced by one single patient. Two SAEs leading to hospitalization (1 in placebo and 1 in CJM112 150 mg group) were not considered related to study drug.

In the multiple dose group, a slightly higher rate of non-serious infections was observed in the CJM112 dose groups with a tendency for dose-related increase. However all infections were of only mild or moderate (Grades 1-2) severity. The majority were upper respiratory tract infections. Two SAEs in one patient in the 150 mg high frequency group during the multi-dose portion of the study both occurring after post-surgery complications were not considered to be related to treatment with study drug.

Cardiac events (one each in SAD Placebo, in 150 mg high and 50 mg MD groups) were mild and transient with short durations over a few minutes only (tachycardia, palpations). No other specific pattern of adverse events was obvious from the safety evaluation of the study.

Pharmacokinetics (total CJM112) - As expected for an IgG1 type antibody, the mean apparent total body clearance (CL/F) for CJM112 in Psoriasis patients was low (0.28-0.59 L/day), fairly consistent across the dose range (Part I), and indicative of linear pharmacokinetics for CJM112. After sc dosing, median Tmax was 3.0 to 7.1 day. Overall, in this study (Part I) the elimination half-life for CJM112 was 17 to 19 day.

Pharmacodynamics (total IL17A) - The extent and duration of free IL-17A capture by CJM112 (Part I and II) and by secukinumab (Part II) was assessed through the time course of total IL-17A concentration in serum. Target engagement was demonstrated in all cohorts through a slow and saturable accumulation of total IL17A concentration in serum (accumulation of the CJM112-IL17A

complexes). These profiles were characteristic of a slow elimination of the CJM112-IL17A complex (taking on the elimination of the drug), a slow turnover of the ligand and a long duration of IL-17A capture. As expected, increasing the dose led to an increase in the duration of target capture by CJM112 (Part I). In Part II, sustained target engagement was demonstrated in all cohorts for the entire treatment period.

Immunogenicity - In Part I, four patients (14.3%) treated with CJM112 were ADA-positive (patients with at least one treatment induced or boosted ADA-positive sample at any time during the treatment or follow-up observation period). ADAs may have affected the PK profile of one patient in the 50 mg cohort, and an effect on the PASI profile cannot be excluded. For two ADA-positive patients in the 150 mg cohort, and for the one in the 450 mg cohort, ADAs did not appear to have affected their PASI profiles when compared to other patients in the same cohort.

In Part II (MD), six patients (14.3%) treated with CJM112 were ADA-positive and the frequency of immunogenicity positive patients appeared to correlate negatively with the dose, with 5/11 (45.5%), 0/10, 1/10 (10%) and 0/11 patients in the 15 mg, 50 mg, 150 mg-low and 150 mg-high cohort, respectively. For 3 patients in the 15 mg cohort, while the positive ADA response was generally characterized with low titers, it cannot be excluded that the ADA response has had a consequence on the target capture profile or on the PASI reduction time course. For the ADA-positive patient in the 150 mg low cohort, the presence of ADAs is unlikely to have affected the PASI reduction time course. None of the patients in the secukinumab cohort had anti-secukinumab antibodies.

The presence of anti-CJM112 antibodies in Part I and II, was not associated with an immune related safety signal.

Date of Clinical Trial Report

12 July 2016