Sponsor

Novartis

Generic Drug Name

KRP203

Therapeutic Area of Trial

Active subacute cutaneous lupus erythematosus (SCLE)

Approved Indication

Investigational

Protocol Number

CKRP203A2202

Title

A multi-center, double-blind, placebo controlled, proof of concept study to evaluate the efficacy and tolerability of KRP203 in patients with active subacute cutaneous lupus erythematosus.

Study Phase

Phase II

Study Start/End Dates

29-Mar-2011 to 20-Oct-2012

Early Termination: 21-Feb-2013. Termination was based on the results of the first interim analysis on 10 patients who completed 12 weeks of treatment (eight patients on KRP203 and two patients on placebo). The results showed that KRP203 was safe and well-tolerated and no increased risk was identified. However, due to the unexpected high clinical response rate in the placebo group as estimated by the CLASI (cutaneous lupus erythematosus disease area and severity index), it was deemed that there was very low probability to reach a positive PoC if the study continued to enroll all patients planned for this study (n=24 for 20 completers). At the time of early termination (21-Feb-2013) no patients were receiving the study drug.

Study Design/Methodology

Multi-center, randomized, double-blind, parallel, placebo controlled proof of concept study to evaluate the efficacy, safety and tolerability of KRP203 in patients with SCLE. To minimize the initial negative chronotropic effects of KRP203, and any associated potential risks such as bradycardia and AV-blocks, a dose-titration scheme was used with doses of 0.3 mg qd (Days 1-4), 0.6 mg qd (Days 5-8), 0.9 mg qd (Days 9-12) and 1.2 mg qd from Day 13 to Day 84. The dose increment was selected based on the SAD and MAD study data indicating that 0.3 mg qd had no clear PD effect with regards to bradycardia. Patients were randomized to KRP203 or placebo and had one treatment period of 12 weeks followed by a 4 week evaluation period. Responders (defined by changes in CLASI) were followed up for a further 8 weeks.

Centers

Six centers in 2 countries; Germany (4), Greece (2)

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

Oral tablets of KRP203 0.1 mg, 0.4 mg and 1.0 mg or matching placebo tablets once daily:

- Day 1 to Day 4: 0.3 mg (3 x 0.1 mg capsules or 3 x matching placebo capsules)
- Day 5 to Day 8: 0.6 mg (1 x 0.4 mg plus 2 x 0.1 mg capsules or 3 x matching placebo capsules)
- Day 9 to Day 12: 0.9 mg (2 x 0.4 mg plus 1 x 0.1 mg capsules or 3 x matching placebo capsules)
- Day 13 to Day 84: 1.2 mg (1 x 1.0 mg plus 2 x 0.1 mg capsules or 3 x matching placebo capsules)

Statistical Methods

All safety, tolerability, demographic and baseline assessments were listed and summarized. Graphical summaries were provided for cardiac safety data, ESR, CRP and routine auto antibodies.

Cardiac safety data: ECG data, HR data and the frequency of atrio-ventricular (AV) blocks and pronounced bradycardia (heart rate below 40 bpm for longer than 6 sec) events were tabulated and displayed graphically.

All efficacy variables was listed and summarized in tabular and graphical forms. Individual graphical profiles were also produced.

Post treatment CLASI was plotted against baseline CLASI for each treatment and the respective correlations were determined.

All biomarker data was listed and summarized by treatment in tabular and graphical forms.

Leukocyte subsets were listed, summarized by treatment in tabular and graphical forms.

Fraction from pre-dose in absolute lymphocyte count was calculated for each time point, listed and summarized. Subject's minimum absolute lymphocyte count over the study period, calculated as fraction from the pre-dose value ("minimum fraction from pre-dose") was analyzed using a linear model and the mean and 95% CI was presented in tabular and graphical formats.

Inferential analysis

An analysis of covariance (ANCOVA) was used to analyze the primary endpoint and to make inferences about the difference between KRP203 and placebo in terms of efficacy. The following probabilities were determined:

• The probability that the true decrease induced by KRP203 in mean CLASI at 12 weeks was at least 5 points;

• The probability that KRP203 was superior to placebo in terms of the difference from baseline in CLASI.

These were represented graphically using probability curves.

The effect of the use of antimalarials was explored.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male and female patients between 18-65 (inclusive) years of age who were defined by the Investigator as having SCLE based on the typical clinical picture and the characteristic features as described by at least three months before study entry (Screening). The Investigator decided if a confirmatory biopsy was required.
2. The patients were required to demonstrate moderate to severe active skin disease at Baseline and have an activity score of CLASI ≥ 6, with at least 2 points in at least 3 different anatomical locations for erythema or scale/hypertrophy.
3. Patients were required to have failed systemic therapy such as a full dose of an antimalarial agent (hydroxychloroquine, chloroquine or quinacrine) or a combination of lower doses of antimalarials, prior to Screening. A failed response was considered to be one or more of the following:
    a. Inadequate clinical response after at least 12 weeks of therapy
    b. Loss of clinical response to antimalarial therapy
    c. Toxicity in response to antimalarial therapy that required discontinuation of treatment.

Exclusion criteria

1. Patients with preexisting nephritis, central nervous or pulmonary involvement or any major internal organ damage, either related or unrelated to lupus, which were deemed by the Investigator as clinically significant. Patients with signs or symptoms of other autoimmune diseases such as SLE or Sjogren`s syndrome were allowed to enter the study at the Investigator`s discretion.
2. Patients who had been treated with:

a. cyclophosphamide within 24 weeks prior to randomization.
b. immunoglobulins such as intravenous immunoglobulin therapy within 12 weeks prior to randomization.
c. Rituximab or any B cell depleting therapy within 24 weeks prior to randomization. Patient having received such therapies in the last 12 months must have had a B cell count in the normal rage.
d. A medium or high dose (≥ 1 mg prednisone or equivalent per body weight kg) corticosteroid therapy in the last 8 weeks prior to randomization.
e. TNF-alpha blocking biologic therapies such as etanercept within the last 4 weeks prior to randomization or infliximab or adalimumab within the last 12 weeks prior to randomization.
f. Any other immunosuppressive or immunomodulatory therapy such as methotrexate, azathioprine, cyclosporin A or mycophenolate, thalidomide, retinoids or dapsone in the last 4 weeks prior to randomization.
g. Any monoclonal antibody or immunosuppressive treatments with effects potentially lasting over 6 months as judged by the Investigator, within 12 months prior to randomization.
h. Total lymphoid irradiation or bone marrow transplantation.

3. Pregnant, planning to get pregnant, and/or lactating females or males planning to father a child within time period of the study or subsequent exclusionary period

Participant Flow

	KRP203 1.2 mg qd N=8 n (%)	Placebo N=2 n (%)	Total N=10 n (%)
Patients			
Completed	6 (75.0)	2 (100.0)	8 (80.0)
Discontinued	2 (25.0)	0 (0.0)	2 (20.0)
Main cause of discontinuation			
Abnormal laboratory value(s)	2 (25.0)	0 (0.0)	2 (20.0)

Baseline Characteristics

		KRP203 1.2 mg qd N=8	Placebo N=2	Total N=10
Age (years)	Mean (SD)	44.8 (9.18)	39.5 (16.26)	43.7 (9.99)
	Median	47.0	39.5	47.0
	Range	29, 54	28, 51	28, 54
Gender - n (%)	Male	3 (37.5)	1 (50.0)	4 (40.0)
	Female	5 (62.5)	1 (50.0)	6 (60.0)
Race - n (%)	Caucasian	8 (100.0)	2 (100.0)	10 (100.0)
Ethnicity - n (%)	Other	8 (100.0)	2 (100.0)	10 (100.0)
Weight (kg)	Mean (SD)	76.4 (14.97)	70.0 (12.73)	75.1 (14.12)
	Median	76.2	70.0	76.2
	Range	54.0, 96.0	61.0, 79.0	54.0, 96.0
Height (cm)	Mean (SD)	170.0 (11.16)	173.0 (11.31)	170.6 (10.62)

		KRP203 1.2 mg qd N=8	Placebo N=2	Total N=10
	Median	167.5	173.0	167.5
	Range	156, 185	165, 181	156, 185
BMI (kg/m ^{2})	Mean (SD)	26.41 (4.75)	23.3 (1.21)	25.8 (4.41)
	Median	25.5	23.3	24.4
	Range	22.2, 36.6	22.4, 24.1	22.2, 36.6

Outcome measures

Primary Outcome Result(s)

Change from Baseline in the CLASI activity score.

		Change from baseline in total activity score					
Treatment		DAY15	DAY36	DAY57	DAY84	DAY113	EOS
KRP203 1.2 mg qd	n	8	6	6	6	4	8
	mean	-2.5	-4.7	-10.2	-10.5	-15.0	-7.3
	SD	7.78	6.77	7.76	5.96	7.87	8.70
	minimum	-17	-17	-18	-17	-23	-19
	median	0.5	-2.5	-11.0	-12.0	-15.5	-7.5
	maximum	7	2	0	-1	-6	4
Placebo	n	2	2	2	2	2	2
	mean	-15.0	-22.5	-24.0	-26.0	-27.0	-27.5
	SD	2.83	9.19	11.31	8.49	7.07	6.36
	minimum	-17	-29	-32	-32	-32	-32
	median	-15.0	-22.5	-24.0	-26.0	-27.0	-27.5
	maximum	-13	-16	-16	-20	-22	-23

Summary statistics for posterior distribution for the change from Baseline in the CLASI activity score at the end of 12 weeks for KRP203 vs. placebo.

Treatment effect / contrast	Summaries of the posterior distribution					
	mean	sd	2.5%	25%	50%	75%	97.5%
KRP203 1.2 mg qd	-10.99	1.694	-14.37	-12.05	-10.98	-9.92	-7.63
Placebo	-24.56	2.928	-30.47	-26.36	-24.54	-22.74	-18.75
KRP203 1.2 mg qd - Placebo	13.57	3.393	6.75	11.50	13.54	15.65	20.46

Sigma:	3.57
Beta:	-0.4224
P(KRP203 1.2 mg qd <= -5):	99.9%
P(KRP203 1.2 mg qd - Placebo < 0):	0.1%

Secondary Outcome Result(s)

The SLEDAI (systemic lupus erythematosus disease activity index) score was used to monitor the changes in systemic features of SCLE upon treatment with KRP203.

		SLEDAI score					
Treatment		BAS	DAY15	DAY36	DAY57	DAY84	DAY113
EOS							
KRP203 1.2 mg qd	n	8	8	6	6	6	4
8							
	mean	0.8	0.8	0.0	0.0	0.0	0.0
1.3							
	SD	1.49	1.49	0.00	0.00	0.00	0.00
2.38							
	minimum	0	0	0	0	0	0
0							
	median	0.0	0.0	0.0	0.0	0.0	0.0
0.0							
	maximum	4	4	0	0	0	0
6							
Placebo	n	2	2	2	2	2	2
2							
	mean	2.0	0.0	2.0	3.0	2.0	2.0
2.0							
	SD	2.83	0.00	2.83	1.41	2.83	2.83
2.83							
	minimum	0	0	0	2	0	0
0							
	median	2.0	0.0	2.0	3.0	2.0	2.0
2.0							
	maximum	4	0	4	4	4	4
4							

		Change from baseline in SLEDAI score					
Treatment		DAY15	DAY36	DAY57	DAY84	DAY113	EOS
KRP203 1.2 mg qd	n	8	6	6	6	4	8
	mean	0.0	-0.3	-0.3	-0.3	-0.5	0.5
	SD	0.00	0.82	0.82	0.82	1.00	2.33
	minimum	0	-2	-2	-2	-2	-2
	median	0.0	0.0	0.0	0.0	0.0	0.0
	maximum	0	0	0	0	0	6
Placebo	n	2	2	2	2	2	2
	mean	-2.0	0.0	1.0	0.0	0.0	0.0
	SD	2.83	0.00	1.41	0.00	0.00	0.00
	minimum	-4	0	0	0	0	0
	median	-2.0	0.0	1.0	0.0	0.0	0.0
	maximum	0	0	2	0	0	0

The intensity of SCLE was assessed on a 100 mm VAS (Visual Analogue Scale) ranging from 0 (nothing) to 100 (most severe) by both the blinded Investigator (Physician Global Activity) and the patient (Patient Global Activity) on VAS of global skin health.

		Patient score					
Treatment		BAS	DAY15	DAY36	DAY57	DAY84	DAY113
EOS							
KRP203 1.2 mg qd	n	8	8	6	6	6	3
8							
	mean	61.6	40.5	41.7	28.7	36.0	26.3
57.3							
	SD	38.36	34.64	37.03	23.25	24.23	16.50
33.24							
	minimum	1	0	0	0	7	8
12							
	median	73.0	31.5	32.0	20.5	35.5	31.0
57.0							
	maximum	100	100	90	63	77	40
100							
Placebo	n	2	2	2	2	2	2
2							
	mean	58.5	15.5	4.0	23.0	2.0	1.8
8.0							
	SD	9.19	14.85	1.41	32.53	1.41	2.47
11.31							
	minimum	52	5	3	0	1	0
0							
	median	58.5	15.5	4.0	23.0	2.0	1.8
8.0							
	maximum	65	26	5	46	3	4
16							

		Physician score					
Treatment		BAS	DAY15	DAY36	DAY57	DAY84	DAY113
EOS							
KRP203 1.2 mg qd	n	8	8	6	6	6	4
8							
	mean	51.3	38.4	45.2	29.3	32.8	37.5
47.0							
	SD	33.68	31.15	30.45	11.72	17.27	25.38
28.94							
	minimum	10	7	14	17	21	7
10							
	median	63.0	30.5	33.0	25.0	25.0	39.0
45.0							
	maximum	91	100	84	47	65	65
90							
Placebo	n	2	2	2	2	2	2
2							

	mean	63.5	25.5	4.0	6.5	1.0	0.2
0.0							
	SD	2.12	31.82	2.83	9.19	1.41	0.21
0.00							
	minimum	62	3	2	0	0	0
0							
	median	63.5	25.5	4.0	6.5	1.0	0.2
0.0							
	maximum	65	48	6	13	2	0
0							

Change from baseline in Patient score

Treatment		DAY15	DAY36	DAY57	DAY84	DAY113	EOS
KRP203 1.2 mg qd	n	8	6	6	6	3	8
	mean	-21.1	-16.2	-29.2	-21.8	-26.3	-4.4
	SD	25.64	30.20	29.50	38.16	20.74	45.53
	minimum	-63	-73	-68	-70	-45	-57
	median	-16.5	-5.5	-28.5	-26.5	-30.0	-13.5
	maximum	8	7	6	42	-4	99
Placebo	n	2	2	2	2	2	2
	mean	-43.0	-54.5	-35.5	-56.5	-56.8	-50.5
	SD	24.04	7.78	23.33	7.78	6.72	2.12
	minimum	-60	-60	-52	-62	-62	-52
	median	-43.0	-54.5	-35.5	-56.5	-56.8	-50.5
	maximum	-26	-49	-19	-51	-52	-49

Change from baseline in Physician score

Treatment		DAY15	DAY36	DAY57	DAY84	DAY113	EOS
KRP203 1.2 mg qd	n	8	6	6	6	4	8
	mean	-12.9	-6.2	-22.0	-18.5	-23.0	-4.3
	SD	32.77	25.15	24.58	24.98	15.71	33.03
	minimum	-63	-42	-44	-49	-42	-40
	median	0.0	2.5	-32.0	-28.0	-23.0	-10.5
	maximum	26	15	11	14	-4	65
Placebo	n	2	2	2	2	2	2
	mean	-38.0	-59.5	-57.0	-62.5	-63.4	-63.5
	SD	33.94	4.95	7.07	0.71	1.91	2.12
	minimum	-62	-63	-62	-63	-65	-65
	median	-38.0	-59.5	-57.0	-62.5	-63.4	-63.5
	maximum	-14	-56	-52	-62	-62	-62

Safety Results

Adverse Events by System Organ Class

	KRP203 1.2 mg qd N=8	Placebo N=2	Total N=10
	n (%)	n (%)	n (%)
Patients with AE(s)	7 (87.5)	1 (50.0)	8 (80.0)
System organ class			
Gastrointestinal disorders	3 (37.5)	1 (50.0)	4 (40.0)
General disorders and administration site conditions	1 (12.5)	1 (50.0)	2 (20.0)
Musculoskeletal and connective tissue disorders	2 (25.0)	0	2 (20.0)
Nervous system disorders	1 (12.5)	1 (50.0)	2 (20.0)
Respiratory, thoracic and mediastinal disorders	1 (12.5)	1 (50.0)	2 (20.0)
Blood and lymphatic system disorders	1 (12.5)	0	1 (10.0)
Ear and labyrinth disorders	1 (12.5)	0	1 (10.0)
Infections and infestations	0	1 (50.0)	1 (10.0)
Investigations	1 (12.5)	0	1 (10.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (12.5)	0	1 (10.0)
Skin and subcutaneous tissue disorders	1 (12.5)	0	1 (10.0)

Most Frequently Reported AEs Overall by Preferred Term n (%)

	KRP203 1.2 mg qd N=8	Placebo N=2	Total N=10
	n (%)	n (%)	n (%)
Patients with AE(s)	7 (87.5)	1 (50.0)	8 (80.0)
Preferred term			
Abdominal pain upper	1 (12.5)	0	1 (10.0)
Arthralgia	1 (12.5)	0	1 (10.0)
Back pain	1 (12.5)	0	1 (10.0)
Cough	0	1 (50.0)	1 (10.0)
Dermatitis contact	1 (12.5)	0	1 (10.0)
Dry mouth	1 (12.5)	0	1 (10.0)
Fatigue	0	1 (50.0)	1 (10.0)
Flank pain	1 (12.5)	0	1 (10.0)
Headache	0	1 (50.0)	1 (10.0)
Influenza	0	1 (50.0)	1 (10.0)
Influenza like illness	1 (12.5)	0	1 (10.0)
Lymphocyte count decreased	1 (12.5)	0	1 (10.0)
Lymphopenia	1 (12.5)	0	1 (10.0)
Migraine	1 (12.5)	0	1 (10.0)
Musculoskeletal pain	1 (12.5)	0	1 (10.0)
Nausea	0	1 (50.0)	1 (10.0)
Oropharyngeal pain	1 (12.5)	0	1 (10.0)
Skin papilloma	1 (12.5)	0	1 (10.0)
Toothache	1 (12.5)	0	1 (10.0)
Vertigo	1 (12.5)	0	1 (10.0)
Vomiting	0	1 (50.0)	1 (10.0)

Serious Adverse Events and Deaths

	KRP203 1.2 mg qd N=8	Placebo N=2	Total N=10
	n (%)	n (%)	n (%)
Patients with AE(s)	7 (87.5)	1 (50.0)	8 (80.0)
Deaths	0	0	0
SAE(s)	1 (12.5)	0	1 (10.0)
Discontinued due to SAE(s)	1 (12.5)	0	1 (10.0)

Other Relevant Findings

Mean (SD) pharmacokinetic parameters of KRP203

Compound: KRP203, Matrix: Blood, Analyte: KNF-451

Profile Day	Scheduled timepoint	Statistic	Concentration (pg/mL)
-7		n	6
		Mean (SD)	20.5 (50.2)
		CV% mean	244.9
		Geo-mean	
		CV% geo-mean	
		Median	0
		[Min; Max]	[0; 123]
8	0 pre-dose	n	5
		Mean (SD)	531 (188)
		CV% mean	35.5
		Geo-mean	506
		CV% geo-mean	35.2
		Median	488
		[Min; Max]	[352; 816]
	6 hours post-dose	n	1
		Mean (SD)	357
		CV% mean	
		Geo-mean	357
		CV% geo-mean	
		Median	357
		[Min; Max]	[357; 357]
15	0 pre-dose	n	7
		Mean (SD)	1060 (531)
		CV% mean	50.0
		Geo-mean	942
		CV% geo-mean	59.3
		Median	931
		[Min; Max]	[392; 1910]
	6 hours post-dose	n	2
		Mean (SD)	1110 (35.4)
		CV% mean	3.2
		Geo-mean	1100
		CV% geo-mean	3.2
		Median	1110
		[Min; Max]	[1080; 1130]
36	0 pre-dose	n	3
		Mean (SD)	1180 (535)
		CV% mean	45.3
		Geo-mean	1090
		CV% geo-mean	55.7
		Median	1260
		[Min; Max]	[610; 1670]

36	6 hours post-dose	n	1
		Mean (SD)	617
		CV% mean	
		Geo-mean	617
		CV% geo-mean	
		Median	617
		[Min; Max]	[617; 617]
57	0 pre-dose	n	3
		Mean (SD)	1270 (772)
		CV% mean	61.0
		Geo-mean	1110
		CV% geo-mean	70.0
		Median	1090
		[Min; Max]	[597; 2110]
	6 hours post-dose	n	3
		Mean (SD)	1480 (858)
		CV% mean	57.8
		Geo-mean	1310
		CV% geo-mean	69.4
		Median	1380
		[Min; Max]	[684; 2390]
84		n	4
		Mean (SD)	43.5 (87.0)
		CV% mean	200.0
		Geo-mean	
		CV% geo-mean	
		Median	0
		[Min; Max]	[0; 174]
	0 pre-dose	n	4
		Mean (SD)	1130 (741)
		CV% mean	65.8
		Geo-mean	940
		CV% geo-mean	81.0
		Median	1010
		[Min; Max]	[466; 2020]
	6 hours post-dose	n	1
		Mean (SD)	1610
		CV% mean	
		Geo-mean	1610
		CV% geo-mean	
		Median	1610
		[Min; Max]	[1610; 1610]

CV% mean = Coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt(exp(variance for log transformed data)-1)*100

Compound: KRP203, Matrix: Blood, Analyte: KRP203

Profile Day	Scheduled timepoint	Statistic	Concentration (pg/mL)
-7		n	2
		Mean (SD)	0 (0)
		CV% mean	
		Geo-mean	
		CV% geo-mean	
		Median	0
		[Min; Max]	[0; 0]
8	0 pre-dose	n	3
		Mean (SD)	463 (63.0)
		CV% mean	13.6
		Geo-mean	460
		CV% geo-mean	13.4
		Median	445
		[Min; Max]	[411; 533]
15	0 pre-dose	n	3
		Mean (SD)	1090 (99.1)
		CV% mean	9.1
		Geo-mean	1080
		CV% geo-mean	9.2
		Median	1100
		[Min; Max]	[983; 1180]
36	0 pre-dose	n	1
		Mean (SD)	1210
		CV% mean	
		Geo-mean	1210
		CV% geo-mean	
		Median	1210
		[Min; Max]	[1210; 1210]
57	0 pre-dose	n	2
		Mean (SD)	1340 (576)
		CV% mean	42.9
		Geo-mean	1280
		CV% geo-mean	46.6
		Median	1340
		[Min; Max]	[935; 1750]
	6 hours post-dose	n	2
		Mean (SD)	1760 (884)
		CV% mean	50.4
		Geo-mean	1640
		CV% geo-mean	56.5
		Median	1760
		[Min; Max]	[1130; 2380]
84		n	4
		Mean (SD)	35.3 (70.5)
		CV% mean	200.0
		Geo-mean	
		CV% geo-mean	
		Median	0

	[Min; Max]	[0; 141]
0 pre-dose	n	4
	Mean (SD)	953 (669)
	CV% mean	70.2
	Geo-mean	782
	CV% geo-mean	84.9
	Median	810
	[Min; Max]	[361; 1830]
6 hours post-dose	n	1
	Mean (SD)	1030
	CV% mean	
	Geo-mean	1030
	CV% geo-mean	
	Median	1030
	[Min; Max]	[1030; 1030]

CV% mean = Coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt(exp(variance for log transformed data)-1)*100

Date of Clinical Trial Report

18 Sep 2013

Date Inclusion on Novartis Clinical Trial Results Database

5 Oct 2013

Date of Latest Update

19 Sep 2013