Sponsor

Novartis,
Kyorin Pharmaceutical Co.,LTD.

Generic Drug Name

KRP203

Therapeutic Area of Trial

Ulcerative colitis

Approved Indication

Not applicable

Protocol Number

CKRP203A2201

Title

A multi-center, double-blind, placebo controlled, parallel group, proof of concept study to evaluate the efficacy, safety and tolerability of KRP203 in patients with moderately active refractory ulcerative colitis

Study Phase

Phase II

Study Start/End Dates

09 Dec 2010 to 02 May 2012. Terminated early for meeting the pre-defined futility criteria at first interim analysis.

Study Design/Methodology

This was a multi-center, double-blind, placebo controlled, parallel group, proof of concept study to evaluate the efficacy, safety and tolerability of KRP203 in patients with moderately active refractory ulcerative colitis.

Part A: Patients with moderately active, treatment refractory ulcerative colitis were enrolled into Part A and randomly assigned to KRP203 or placebo at a 2:1 ratio. The randomization was stratified by steroid intake at baseline (yes/no).

Part B: Based on the read out at an interim analysis, one of the following options were required to be chosen for Part B:

Option 1 (in case of sufficient evidence for efficacy at the interim analysis): The remaining subjects were planned to be randomized to receive lower doses of KRP203 (0.6 mg or 0.9 mg at a 1:1 ratio). Subjects were to receive KRP203 over a period of 56 days.

Option 2 (in case of inconclusive data at the interim analysis): Same design as in Part A

Centers

10 centers in 5 countries: Belgium (2), Sweden (2), Switzerland (2), Germany (2), Hungary (2)

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

KRP203 0.1 mg, 0.4 mg, 1 mg (used for dose up-titration to reach the target dose of 1.2 mg within 12 days of treatment initiation)

Matching placebo capsules

Statistical Methods

Bayesian posterior probabilities were calculated for three hypotheses of interest: H0: no effect, H1: minimal relevant effect, and H2: very promising effect. H0 corresponds to a remission rate under KRP203 that is not larger than under placebo, H1 corresponds to a remission rate of at least 20 percentage points more than under placebo, and H2 corresponds to a remission rate of at least 50 percentage points more than under placebo.

The study was to be considered a positive sign for efficacy if the posterior probability against H0 was at least 95% and the posterior probability in favor of H1 was at least 50%, at the IA or the EOS. The posterior probability of H2 was also displayed.

The prior probability distribution for placebo drew information worth 20 patients from previous studies that used the same patient population. The historical response rate was estimated to be 12%, so the prior is a Beta (2.4, 17.6) distribution. For the KRP203 prior distribution a "flat" non-informative probability distribution Beta (1, 1) was assumed.

The change from baseline in the Partial Mayo (clinical activity) score at Week-8 was considered a key variable. A Bayesian approach similar to the primary analysis was applied to this endpoint. For the change from baseline in the Partial Mayo score, H0 correspond to a change under KRP203 that was not larger than under placebo, H1 correspond to a change of at least 1.5 points more than under placebo, and H2 correspond to a change of at least 2 x 1.5 = 3.0 points more than under placebo.

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Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

•Active disease defined by a partial Mayo score of 5-9 and a modified Baron score of at least 2 upon endoscopic examination with disease extending at least 25 cm from the anal verge

•Subjects must have inadequately responded or intolerance to 5-ASA therapy

Exclusion Criteria:

•Subjects receiving treatment for UC (other than 5-ASAs and steroids) within the time frame mentioned in protocol

•Past or recent history of significant medical illness and/or clinically significant lab abnormalities including but not limited to hematology, clinical chemistry, urine analysis, ECG abnormalities, HIV, Hepatitis B/C

•Presence or history of underlying metabolic, endocrine, hematologic, pulmonary, ophthalmic, cardiac, blood, renal, hepatic, infectious, psychiatric or any medically unstable condition, as assessed by the primary treating physician which, in the opinion of the investigator, would immunocompromise the subject and/or place the subject at unacceptable risk for participation in a study of an immunomodulatory therapy Other protocol-defined inclusion/exclusion criteria apply

Participant Flow

	KRP203 1.2 mg N=17 n (%)	**Placebo N=10 n (%)**	**Total N=27 n (%)**
Patients			
Completed	9 (52.9)	5 (50.0)	14 (51.9)
Discontinued	8 (47.1)	5 (50.0)	13 (48.1)
Main cause of discontinuation			
Adverse Event(s)	1 (5.9)	1 (10.0)	2 (7.4)
Abnormal laboratory value(s)	1 (5.9)	0	1 (3.7)
Unsatisfactory therapeutic effect	5 (29.4)	4 (40.0)	9 (33.3)
Subject withdrew consent	1 (5.9)	0	1 (3.7)

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Baseline Characteristics

		KRP203 1.2 mg N=17	Placebo N=10	Total N=27
Age (years)	Mean (SD)	40.1 (16.23)	31.7 (8.53)	37.0 (14.29)
	Median	37.0	28.5	36.0
	Range	19, 65	20, 46	19, 65
Height (cm)	Mean (SD)	171.1 (6.76)	169.6 (7.71)	170.5 (7.01)
	Median	172.0	170.0	170.0
	Range	160, 180	155, 182	155, 182
Weight (kg)	Mean (SD)	69.15 (13.542)	72.13 (12.212)	70.26 (12.909)
	Median	69.10	74.00	72.60
	Range	49.0, 102.9	50.0, 90.4	49.0, 102.9
BMI (kg/m2)	Mean (SD)	23.452 (3.2020)	25.343 (5.7586)	24.153 (4.3190)
	Median	23.301	25.152	23.356
	Range	18.90, 31.76	17.75, 37.63	17.75, 37.63
Sex - n(%)	Male	11 (64.7%)	4 (40.0%)	15 (55.6%)
	Female	6 (35.3%)	6 (60.0%)	12 (44.4%)
Race - n(%)	Caucasian	16 (94.1%)	9 (90.0%)	25 (92.6%)
	Black		1 (10.0%)	1 (3.7%)
	Other	1 (5.9%)		1 (3.7%)
Ethnicity - n(%)	Other	17 (100.0%)	10 (100.0%)	27 (100.0%)

Primary Outcome Result(s)

A total of 14 KRP203-treated patients and 8 placebo-treated patients qualified for the primary efficacy analysis. Treatment response was defined as clinical remission after 8 weeks of treatment. Remission was defined as a partial Mayo score of 0 or 1 with a score of 0 in the rectal bleeding dimension, and a modified Baron score of 0 or 1 (by sigmoidoscopy). All patients receiving at least 28 days of treatment qualified for the primary efficacy analysis.

Responder status at week 8 by treatment group

	No. of patients in remission / No. of evaluable patients (%)
KRP203	2 / 14 (14)
Placebo	0 / 8 (0)

Baysian analysis of responder status at week 8

Probability for rejecting H0 (%)	Probability in favor of H1 (%)
83.7	17.5

Secondary Outcome Result(s)

Summary statistics of absolute lymphocyte counts (ALC) in KRP203 treatment group

	Time of assessment (days)				
	7	15	28	56	End of study
	N=14	N=14	N=11	N=8	N=13
Mean ALC (x 10^9/L)	1.082	0.740	0.605	0.648	1.164
Change from baseline (x 10^9/L)	-0.636	-1.009	-1.098	-1.179	-0.395

Summary statistics of blood trough concentrations of KRP203-P and KRP203 in KRP203 treatment group

	Time of assessment (days)				
	1	7	15	28	56
KRP203-P (ng/ml)	0 (N=15)	0.679 (n=14)	1.57 (n=15)	2.27 (n=13)	3.25 (n=8)
KRP203 (ng/ml)	0 (n=10)	0.566 (n=9)	1.40 (n=10)	2.05 (n=6)	3.42 (n=3)

The absolute change from Baseline in the Partial Mayo score at Week 8 was a key secondary endpoint. A total of 10 KRP203-treated patients and 5 placebo-treated patients qualified for the key secondary efficacy analysis.

Bayesian analysis of Partial Mayo score at Week 8

		Posterior	
	No. of patients	Mean	Standard deviation
KRP203	10	-2.7	1.35
Placebo	5	-1.6	1.91
KRP203 vs Placebo		-1.1	2.33

Probability for rejecting H0 (%)	Probability in favor of H1 (%)	Probability in favor of H2 (%)
67.5	42.5	20.3

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Safety Results

Adverse Events by System Organ Class

	KRP203 1.2 mg N=17 n (%)	Placebo N=10 n (%)	Total N=27 n (%)
Patients with AE(s)	15 (88.2)	9 (90.0)	24 (88.9)
System organ class			
Gastrointestinal disorders	7 (41.2)	4 (40.0)	11 (40.7)
Nervous system disorders	5 (29.4)	2 (20.0)	7 (25.9)
General disorders and administration site conditions	5 (29.4)	1 (10.0)	6 (22.2)
Musculoskeletal and connective tissue disorders	4 (23.5)	2 (20.0)	6 (22.2)
Infections and infestations	4 (23.5)	1 (10.0)	5 (18.5)
Investigations	0 (0.0)	4 (40.0)	4 (14.8)
Skin and subcutaneous tissue disorders	3 (17.6)	1 (10.0)	4 (14.8)
Eye disorders	2 (11.8)	1 (10.0)	3 (11.1)
Blood and lymphatic system disorders	2 (11.8)	0 (0.0)	2 (7.4)
Respiratory, thoracic and mediastinal disorders	2 (11.8)	0 (0.0)	2 (7.4)
Vascular disorders	1 (5.9)	1 (10.0)	2 (7.4)
Endocrine disorders	0 (0.0)	1 (10.0)	1 (3.7)
Hepatobiliary disorders	1 (5.9)	0 (0.0)	1 (3.7)
Metabolism and nutrition disorders	0 (0.0)	1 (10.0)	1 (3.7)
Psychiatric disorders	0 (0.0)	1 (10.0)	1 (3.7)
Surgical and medical procedures	1 (5.9)	0 (0.0)	1 (3.7)

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

	KRP203 1.2 mg N=17 n (%)	Placebo N=10 n (%)	Total N=27 n (%)
Patients with AE(s)	15 (88.2)	9 (90.0)	24 (88.9)
Preferred term			
Headache	4 (23.5)	2 (20.0)	6 (22.2)
Diarrhoea	1 (5.9)	2 (20.0)	3 (11.1)
Nausea	2 (11.8)	1 (10.0)	3 (11.1)
Pruritus	2 (11.8)	1 (10.0)	3 (11.1)
Abdominal pain	1 (5.9)	1 (10.0)	2 (7.4)
Abdominal pain upper	2 (11.8)	0 (0.0)	2 (7.4)
Application site erythema	2 (11.8)	0 (0.0)	2 (7.4)
Arthralgia	1 (5.9)	1 (10.0)	2 (7.4)
Colitis ulcerative	1 (5.9)	1 (10.0)	2 (7.4)
Fatigue	1 (5.9)	1 (10.0)	2 (7.4)
Flatulence	1 (5.9)	1 (10.0)	2 (7.4)
Nasopharyngitis	1 (5.9)	1 (10.0)	2 (7.4)
Ocular hyperaemia	1 (5.9)	1 (10.0)	2 (7.4)

	KRP203 1.2 mg N=17 n (%)	Placebo N=10 n (%)	Total N=27 n (%)
Pyrexia	2 (11.8)	0 (0.0)	2 (7.4)
Acute tonsillitis	1 (5.9)	0 (0.0)	1 (3.7)
Back pain	1 (5.9)	0 (0.0)	1 (3.7)
Bacterial test positive	0 (0.0)	1 (10.0)	1 (3.7)
Blood creatine phosphokinase increased	0 (0.0)	1 (10.0)	1 (3.7)
Bone pain	1 (5.9)	0 (0.0)	1 (3.7)
Colitis	0 (0.0)	1 (10.0)	1 (3.7)
Conjunctival hyperaemia	1 (5.9)	0 (0.0)	1 (3.7)
Cushingoid	0 (0.0)	1 (10.0)	1 (3.7)
Decreased appetite	0 (0.0)	1 (10.0)	1 (3.7)
Diarrhoea haemorrhagic	0 (0.0)	1 (10.0)	1 (3.7)
Diarrhoea infectious	1 (5.9)	0 (0.0)	1 (3.7)
Dizziness	1 (5.9)	0 (0.0)	1 (3.7)
Dry skin	1 (5.9)	0 (0.0)	1 (3.7)
Dyspnoea	1 (5.9)	0 (0.0)	1 (3.7)
Enterocolitis	1 (5.9)	0 (0.0)	1 (3.7)
Flushing	1 (5.9)	0 (0.0)	1 (3.7)
Gastritis	1 (5.9)	0 (0.0)	1 (3.7)
Haemoglobin decreased	0 (0.0)	1 (10.0)	1 (3.7)
Hepatic function abnormal	1 (5.9)	0 (0.0)	1 (3.7)
Hypoaesthesia	1 (5.9)	0 (0.0)	1 (3.7)
Joint swelling	0 (0.0)	1 (10.0)	1 (3.7)
Lacrimation increased	1 (5.9)	0 (0.0)	1 (3.7)
Lymphadenitis	1 (5.9)	0 (0.0)	1 (3.7)
Lymphopenia	1 (5.9)	0 (0.0)	1 (3.7)
Muscular weakness	0 (0.0)	1 (10.0)	1 (3.7)
Musculoskeletal pain	1 (5.9)	0 (0.0)	1 (3.7)
Myalgia	1 (5.9)	0 (0.0)	1 (3.7)
Neck pain	0 (0.0)	1 (10.0)	1 (3.7)
Osteoarthritis	1 (5.9)	0 (0.0)	1 (3.7)
Painful defaecation	1 (5.9)	0 (0.0)	1 (3.7)
Rash	1 (5.9)	0 (0.0)	1 (3.7)
Rhinorrhoea	1 (5.9)	0 (0.0)	1 (3.7)
Sleep disorder	0 (0.0)	1 (10.0)	1 (3.7)
Tendon pain	0 (0.0)	1 (10.0)	1 (3.7)
Thirst	1 (5.9)	0 (0.0)	1 (3.7)
Tooth extraction	1 (5.9)	0 (0.0)	1 (3.7)
Toothache	1 (5.9)	0 (0.0)	1 (3.7)
Upper respiratory tract infection bacterial	1 (5.9)	0 (0.0)	1 (3.7)
Urine analysis abnormal	0 (0.0)	1 (10.0)	1 (3.7)
Vena cava thrombosis	0 (0.0)	1 (10.0)	1 (3.7)
Vomiting	1 (5.9)	0 (0.0)	1 (3.7)

Serious Adverse Events and Deaths

		KRP203 1.2 mg N=17 n	Placebo N=10 n	Total N=27 n
Patients with SAE(s)		2	2	4
System organ class	**Prefered term**			
Infections and infestations	Diarrhoea infectious	1	0	1
Musculoskeletal and connective tissue disorders	Osteoarthritis	1	0	1
Vascular disorders	Venacava thrombosis	0	1	1
Gastrointestinal disorders	Diarrhoea haemorrhagic, diarrhea*	0	1	1

* 4 SAEs of diarrhoea were reported in 1 patient

Date of Clinical Trial Report

19 April 2013

Date Inclusion on Novartis Clinical Trial Results Database

16 May 2013

Date of Latest Update