Sponsor

Novartis

Generic Drug Name

Canakinumab

Trial Indication

Gouty arthritis

Approved Indication

Canakinumab was first registered for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in the United States on 17 Jun 2009. It is indicated in adults and children aged two years and older with Periodic fever syndromes including Cryopyrin-Associated Periodic Syndrome (CAPS), Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS), hyper immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), Familial Mediterranean Fever (FMF); Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA); and patients with Gouty arthritis (GA).

Protocol Number

CACZ885H2357E3

Protocol Title

An open-label extension study of CACZ885H2356E2 and CACZ885H2357E2 on the treatment and prevention of gout flares in patients with frequent flares for whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective.

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

10-Nov-2011 (first patient first visit) to 22-May-2013 (last patient last visit)

Study Design/Methodology

This was an 18-month, multi-center, open-label, clinical extension study. Patients completing earlier second extension studies (CACZ885H2356E2 and CACZ885H2357E2) continued to be treated in this the combined extension 3 study for any new gouty arthritis flare on demand with one subcutaneous (s.c.) injection of canakinumab 150 mg.

Centers

Total of 60 centers in this extension study: Australia (1), Canada (4), Estonia (2), Germany (3), Latvia (1), Lithuania (5), Russia (7), Switzerland (1), Ukraine (2), United States (34).

Objectives:

Primary objectives

The primary objective of this study was to assess the long-term safety and tolerability of canakinumab, particularly with regards to potential consequences of immunosuppression (e.g. serious infections or malignancies) and immunogenicity after multiple treatments.

Secondary objectives

The Secondary objectives of this study were:

1. To evaluate the long-term efficacy of canakinumab, defined as frequency of new flares, patient's assessment of gout pain intensity (Likert scale) over time, patient's global assessment of response to treatment (Likert scale) over time
2. To evaluate the efficacy of canakinumab with regards to inflammatory markers (high sensitivity C-reactive protein [hsCRP])
3. To evaluate the immunogenicity of canakinumab
4. To evaluate the safety in the concomitant use of canakinumab with different urate lowering therapy regimens

Test Product, Dose, and Mode of Administration

All patients were to receive canakinumab 150 mg subcutaneous (s.c.), pre-filled syringe (PFS), on demand upon new flares. Novartis supplied prefilled syringes (PFS) containing ready-to-use 150 mg canakinumab in 1 ml solution for on demand dosing upon new flares.

Statistical Methods

The data analysis was follow-up analysis from the core (H2356 and H2357) and all of the extension studies.

Data were summarized with respect to demographic and baseline characteristics (from the core studies), efficacy and safety observations and measurements, and pharmacokinetic/pharmacodynamics (PK/PD) measurements.

The Safety set was used for the analysis of safety data during the core and the extension studies. Adverse events and serious adverse events are summarized by presenting, for each treatment group, the incidence rate adjusted for the time of exposure (per 100 patient years) for occurrence of each primary system organ class and preferred term. All other information collected (e.g. severity, relationship to study drug) was tabulated and listed as appropriate. In addition, AE (including infections, serious infections or malignancies) were coded using MedDRA dictionary that provided the primary system organ class and preferred term information. A dot-plot of all AEs over time is provided for canakinumab 150 mg s.c patients who were re-treated and for triamcinolone acetonide 40 mg i.m. patients who were treated with canakinumab were provided.

All efficacy analyses were performed using the Full Analysis Set (FAS) or the Modified Analysis Set (MAS). Summary statistics is provided for the flare rate per year by treatment using the MAS. Flare rate is calculated as the number of new gout flares over the period of observation in years. Patient assessment of gout pain intensity (Likert scale), global assessment of response to treatment (Likert scale) is presented with frequency tables by treatment for all patients and for patients who were re-treated using the MAS. Summary statistics is provided for hsCRP presenting absolute values and changes from baseline using the MAS.

The Urate Lowering Therapy (ULT) Optimization Subset1 of the safety set consists of patients initiating or modifying ULT during the conduct of this extension 3 study. The ULT is identified using ATC codes M04AA, M04AB and M04AX based on the ULT treatment initiation or modification in extension 3 study.
The Urate Lowering Therapy (ULT) Optimization Subset2 of the safety set consists of patients initiating or modifying ULT during the conduct of core, E1, E2 or E3 studies.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Patients who have completed the second extension studies CACZ885H2356E2 or CACZ885H2357E2
• Patients treated with canakinumab in the core studies or subsequent extensions

Exclusion Criteria:
• Pregnant or nursing (lactating) women

Participant Flow Table

Patient disposition by treatment (randomized set)

	ACZ885 150mg sc (N=227)		Triam 40mg im (N=229)		
	All ACZ N=227 n (%)	Re-treated with ACZ N=136 n (%)	All Triam N=229 n (%)	Treated with ACZ N=83 n (%)	Total N=456 n (%)
Completed core studies	208 (91.6)	136 (100.0)	208 (90.8)	83 (100.0)	416 (91.2)
Discontinued core studies	19 (8.4)	0 (0.0)	21 (9.2)	0 (0.0)	40 (8.8)
Entered extension 1 studies	174 (76.7)	129 (94.9)	161 (70.3)	83 (100.0)	335 (73.5)
Completed extension 1 studies	165 (72.7)	128 (94.1)	152 (66.4)	83 (100.0)	317 (69.5)
Discontinued extension 1 studies	9 (4.0)	1 (0.7)	9 (3.9)	0 (0.0)	18 (3.9)

	ACZ885 150mg sc (N=227)		Triam 40mg im (N=229)		
	All ACZ N=227 n (%)	Re-treated with ACZ N=136 n (%)	All Triam N=229 n (%)	Treated with ACZ N=83 n (%)	Total N=456 n (%)
Entered extension 2 studies	141 (62.1)	120 (88.2)	131 (57.2)	83 (100.0)	272 (59.6)
Completed extension 2 studies	132 (58.1)	113 (83.1)	117 (51.1)	78 (94.0)	249 (54.6)
Discontinued extension 2 studies	9 (4.0)	7 (5.1)	14 (6.1)	5 (6.0)	23 (5.0)
Entered extension 3 study	87 (38.3)	82 (60.3)	49 (21.4)	49 (59.0)	136 (29.8)
Completed extension 3 study	79 (34.8)	74 (54.4)	43 (18.8)	43 (51.8)	122 (26.8)
Discontinued extension 3 study	8 (3.5)	8 (5.9)	6 (2.6)	6 (7.2)	14 (3.1)
Discontinued core, extension 1, extension 2, or extension 3 study	45 (19.8)	16 (11.8)	50 (21.8)	11 (13.3)	95 (20.8)
Reason for discontinuation					
Adverse event(s)	2 (0.9)	1 (0.7)	5 (2.2)	5 (6.0)	7 (1.5)
Abnormal laboratory value(s)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.4)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	6 (2.6)	0 (0.0)	6 (1.3)
Patient's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient withdrew consent	19 (8.4)	7 (5.1)	17 (7.4)	2 (2.4)	36 (7.9)
Lost to follow-up	18 (7.9)	7 (5.1)	13 (5.7)	2 (2.4)	31 (6.8)
Administrative problems	2 (0.9)	0 (0.0)	4 (1.7)	2 (2.4)	6 (1.3)
Death	2 (0.9)	1 (0.7)	2 (0.9)	0 (0.0)	4 (0.9)
Protocol deviation	1 (0.4)	0 (0.0)	2 (0.9)	0 (0.0)	3 (0.7)

The primary reason for discontinuation as given by the investigator on the study completion eCRF was summarized.
The data are presented according to the original treatment the patients were randomized to.
If patient was randomized to Triam 40mg im and discontinued after switching to ACZ 150mg sc, this discontinuation is shown in both 'All Triam' and 'Treated with ACZ' columns.

Baseline Characteristics

Demographic and other baseline characteristics by treatment (safety set) – CACZ885H2356E2

Demographic variable	Randomized to ACZ885 150mg sc (N=113)		Randomized to Triam 40mg im (N=115)		Total N=228
	All ACZ N=113	Re-treated with ACZ N=69	All Triam N=115	Switched to ACZ N=39	
Sex					
Male	101 (89.4%)	63 (91.3%)	108 (93.9%)	37 (94.9%)	209 (91.7%)
Female	12 (10.6%)	6 (8.7%)	7 (6.1%)	2 (5.1%)	19 (8.3%)
Age (years)					
n	113	69	115	39	228
Mean (SD)	54.0 (11.18)	52.4 (10.19)	54.6 (10.71)	55.3 (12.80)	54.3(10.93)
Median	54.0	52.0	55.0	54.0	54.0
Min, Max	31, 82	33, 78	28, 85	28, 85	28, 85
Age groups					
< 65 years	92 (81.4%)	60 (87.0%)	92 (80.0%)	28 (71.8%)	184 (80.7%)
≥ 65-74 years	16 (14.2%)	8 (11.6%)	21 (18.3%)	9 (23.1%)	37 (16.2%)
≥ 75 years	5 (4.4%)	1 (1.4%)	2 (1.7%)	2 (5.1%)	7 (3.1%)
Race					
Caucasian	93 (82.3%)	59 (85.5%)	96 (83.5%)	38 (97.4%)	189 (82.9%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	3 (2.7%)	3 (4.3%)	3 (2.6%)	1 (2.6%)	6 (2.6%)
Native American	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (0.9%)
Pacific islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	16 (14.2%)	7 (10.1%)	15 (13.0%)	0 (0.0%) [1]	31 (13.6%)
BMI (kg/m2)**					
n	113	69	115	39	228
Mean (SD)	31.84 (4.710)	31.38 (4.673)	31.57 (4.745)	32.24 (4.682)	31.70 (4.719)
Median	31.17	31.17	31.15	32.25	31.16
Min, Max	22.5, 44.2	22.8, 44.2	21.5, 44.5	22.2, 41.2	21.5, 44.5

Demographic and other baseline characteristics by treatment (safety set) – CACZ885H2357E2

Demographic variable	ACZ885 150mg sc (N=112) All ACZ N=112	Re-treated with ACZ N=62	Triam 40mg im (N=114) All Triam N=114	Treated with ACZ N=41	Total N=226
Sex					
Male	100(89.3%)	55(88.7%)	105(92.1%)	37(90.2%)	205(90.7%)
Female	12(10.7%)	7(11.3%)	9(7.9%)	4(9.8%)	21(9.3%)
Age (years)					
n	112	62	114	41	226
Mean	50.6	50.6	52.6	50.6	51.6
SD	12.10	11.60	12.28	12.37	12.21
Median	51.0	51.5	53.0	51.0	52.0
Min	20	20	24	26	20
Max	78	75	79	74	79
Age groups					
< 65 years	96(85.7%)	53(85.5%)	93(81.6%)	34(82.9%)	189(83.6%)
≥65-74 years	14(12.5%)	8(12.9%)	17(14.9%)	7(17.1%)	31(13.7%)
≥ 75 years	2(1.8%)	1(1.6%)	4(3.5%)	0(0.0%)	6(2.7%)
Race					
Caucasian	74(66.1%)	42(67.7%)	80(70.2%)	27(65.9%)	154(68.1%)
Black	26(23.2%)	13(21.0%)	24(21.1%)	9(22.0%)	50(22.1%)
Asian	10(8.9%)	7(11.3%)	9(7.9%)	4(9.8%)	19(8.4%)
Native american	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Pacific islander	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Other	2(1.8%)	0(0.0%)	1(0.9%)	1(2.4%)	3(1.3%)
BMI (kg/m**2)					
n	112	62	114	41	226
Mean	32.08	31.15	31.50	32.98	31.79
SD	6.017	5.802	5.467	6.096	5.740
Median	30.77	30.68	30.86	32.46	30.85
Min	19.5	19.5	21.1	21.1	19.5
Max	45.0	44.9	44.9	44.9	45.0

Age is calculated at Visit 1 using date of birth.
Body Mass Index: BMI (kg/m**2) = weight (kg) / [(height (cm) / 100)**2].

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Results(s)

Flare rate per year: Summary statistics by treatment (Modified Analysis Set)

	ACZ885 150mg sc (N=225)		Triam 40mg im (N=229)	
Statistic	All ACZ N=225	Re-treated with ACZ N=136	All Triam N=229	Treated with ACZ N=83
N	225	136	229	83
Mean	1.109	1.689	2.459	0.996
SD	1.608	1.627	3.701	1.094
Min	0.00	0.33	0.00	0.00
Q1	0.000	0.700	0.000	0.000
Median	0.676	1.310	1.255	0.846
Q3	1.467	2.144	3.765	1.627
Max	12.89	12.89	28.10	5.67

Flare rate is calculated as the number of new flares over the period of observation in years.
Data for flares on Triam 40mg im are presented in 'All Triam' column; data for flares on ACZ885 150mg sc are presented in all other columns.

Flare rate per year: Summary statistics by treatment (ULT optimization Subset1)

	ACZ885 150mg sc (N=29)		Triam 40mg im (N=11)	
Statistic	All ACZ N=29	Re-treated with ACZ N=29	All Triam N=11	Treated with ACZ N=11
N	29	29	11	11
Mean	1.361	1.361	5.787	2.101
SD	0.688	0.688	4.436	1.365
Min	0.66	0.66	2.14	0.82
Q1	0.686	0.686	3.708	1.320
Median	1.018	1.018	4.401	1.725
Q3	1.705	1.705	5.398	2.400
Max	3.38	3.38	17.19	5.67

Flare rate is calculated as the number of new flares over the period of observation in years.
Data for flares on Triam 40mg im are presented in 'All Triam' column; data for flares on ACZ885 150mg sc are presented in all other columns.

Post-baseline flares compared to baseline flare: clinical response in patients who were re-treated with ACZ (Modified Analysis Set)

	ACZ885 150mg sc re-treated with ACZ (N=136)		Triam 40mg im treated with ACZ (N=83)	
Assessment / Timepoint	**Baseline flare**	**Last new flare**	**1st new flare on ACZ**	**Last new flare**
Pain intensity (Likert scale): None or Mild				
Baseline	1 / 135 (0.7)	4 / 135 (3.0)	3 / 83 (3.6)	3 / 83 (3.6)
24 hours post-dose	67 / 128 (52.3)	41 / 128 (32.0)	38 / 80 (47.5)	22 / 80 (27.5)
48 hours post-dose	83 / 124 (66.9)	54 / 124 (43.5)	58 / 80 (72.5)	41 / 80 (51.3)
72 hours post-dose	94 / 130 (72.3)	74 / 130 (56.9)	67 / 80 (83.8)	59 / 80 (73.8)
4 days post-dose	96 / 128 (75.0)	86 / 128 (67.2)	70 / 80 (87.5)	65 / 80 (81.3)
5 days post-dose	100 / 129 (77.5)	93 / 129 (72.1)	71 / 80 (88.8)	64 / 80 (80.0)
6 days post-dose	95 / 127 (74.8)	95 / 127 (74.8)	71 / 79 (89.9)	67 / 79 (84.8)
7 days post-dose	102 / 127 (80.3)	104 / 127 (81.9)	72 / 78 (92.3)	69 / 78 (88.5)
Patient's global assessment of response to treatment: Excellent or Good				
72 hours post-dose	81 / 127 (63.8)	64 / 127 (50.4)	51 / 74 (68.9)	46 / 74 (62.2)
7 days post-dose	96 / 128 (75.0)	86 / 128 (67.2)	65 / 78 (83.3)	62 / 78 (79.5)

At each timepoint only patients with a value at both baseline flare and the post-baseline flare are included.

Safety Results

Exposure adjusted (per 100 patient years) incidence of frequent AEs (> 5 in any treatment group) by primary system organ class (Safety Set)

	ACZ885 150mg sc (N=225)			Triam 40mg im (N=229)		
		Re-treated with ACZ N=136			Treated with ACZ N=83	
	All ACZ N=225 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All Triam N=229 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)
Total	935 (264.6)	307 (388.8)	450 (205.8)	472 (308.8)	182 (296.0)	222 (175.0)
Musculoskeletal and connective tissue disorders	147 (41.6)	36 (45.6)	78 (35.7)	66 (43.2)	30 (48.8)	26 (20.5)
Investigations	126 (35.7)	48 (60.8)	61 (27.9)	72 (47.1)	19 (30.9)	21 (16.6)
Infections and infestations	134 (37.9)	47 (59.5)	67 (30.6)	56 (36.6)	24 (39.0)	33 (26.0)
Metabolism and nutrition disorders	70 (19.8)	23 (29.1)	37 (16.9)	33 (21.6)	12 (19.5)	22 (17.3)
Nervous system disorders	62 (17.5)	19 (24.1)	26 (11.9)	37 (24.2)	16 (26.0)	13 (10.2)
Gastrointestinal disorders	56 (15.8)	19 (24.1)	22 (10.1)	38 (24.9)	13 (21.1)	25 (19.7)
Vascular disorders	53 (15.0)	14 (17.7)	29 (13.3)	24 (15.7)	10 (16.3)	9 (7.1)
Renal and urinary disorders	40 (11.3)	12 (15.2)	21 (9.6)	16 (10.5)	6 (9.8)	9 (7.1)
Cardiac disorders	28 (7.9)	8 (10.1)	13 (5.9)	25 (16.4)	6 (9.8)	10 (7.9)
Injury, poisoning and procedural complications	31 (8.8)	11 (13.9)	15 (6.9)	21 (13.7)	14 (22.8)	7 (5.5)
General disorders and administration site conditions	33 (9.3)	12 (15.2)	10 (4.6)	15 (9.8)	6 (9.8)	11 (8.7)
Skin and subcutaneous tissue disorders	31 (8.8)	15 (19.0)	14 (6.4)	16 (10.5)	7 (11.4)	5 (3.9)
Respiratory, thoracic and mediastinal disorders	26 (7.4)	6 (7.6)	15 (6.9)	14 (9.2)	5 (8.1)	9 (7.1)

Blood and lymphatic system disorders	25 (7.1)	11 (13.9)	7 (3.2)	4 (2.6)	3 (4.9)	8 (6.3)
Psychiatric disorders	15 (4.2)	6 (7.6)	5 (2.3)	13 (8.5)	3 (4.9)	6 (4.7)

Primary system organ classes are sorted by descending frequency of the total number of events observed for all patients.
n = Number of events.
The incidence rate per 100 patient-years (IR/100 pyr) is 100 times (total number of occurrence of events divided by patient-years). It is calculated per SOC level.
Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure until the date of last study day.
(1)1st treatment/re-treatment with ACZ.

Exposure adjusted (per 100 patient years) incidence of frequent AEs (> 5 in any treatment group) by preferred term (Safety Set)

	ACZ885 150mg sc (N=225)			Triam 40mg im (N=229)		
		Re-treated with ACZ N=136			Treated with ACZ N=83	
	All ACZ N=225 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All Triam N=229 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)
Hypertension	42 (11.9)	10 (12.7)	25 (11.4)	20 (13.1)	8 (13.0)	7 (5.5)
Arthralgia	26 (7.4)	5 (6.3)	17 (7.8)	19 (12.4)	7 (11.4)	5 (3.9)
Headache	21 (5.9)	6 (7.6)	6 (2.7)	14 (9.2)	5 (8.1)	2 (1.6)
Upper respiratory tract infection	25 (7.1)	7 (8.9)	16 (7.3)	6 (3.9)	3 (4.9)	5 (3.9)
Back pain	28 (7.9)	6 (7.6)	16 (7.3)	2 (1.3)	1 (1.6)	1 (0.8)
Gout	13 (3.7)	2 (2.5)	10 (4.6)	10 (6.5)	4 (6.5)	5 (3.9)
Osteoarthritis	19 (5.4)	4 (5.1)	9 (4.1)	2 (1.3)	0.0 (0.0)	5 (3.9)
Nasopharyngitis	8 (2.3)	4 (5.1)	2 (0.9)	10 (6.5)	7 (11.4)	7 (5.5)
Pain in extremity	6 (1.7)	2 (2.5)	4 (1.8)	12 (7.8)	7 (11.4)	1 (0.8)
Muscle spasms	5 (1.4)	2 (2.5)	2 (0.9)	11 (7.2)	8 (13.0)	0.0 (0.0)
Influenza	9 (2.5)	1 (1.3)	8 (3.7)	1 (0.7)	0.0 (0.0)	1 (0.8)

Preferred terms are sorted by descending frequency of the total number observed for all patients.
n = Number of events.
The incidence rate per 100 patient-years (IR/100 pyr) is 100 times (total number of occurrence of events divided by patient-years).It is calculated per SOC level.
Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure until the date of last study day.
(1)1st treatment/re-treatment with ACZ

Exposure adjusted (per 100 patient years) incidence of deaths, other serious adverse events or related discontinuations (Safety Set)

	ACZ885 150mg sc (N=225)			Triam 40mg im (N=229)		
		Re-treated with ACZ N=136			Treated with ACZ N=83	
	All ACZ N=225 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All Triam N=229 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)
Any AE(s)	873 (247.0)	285 (360.9)	413 (188.8)	451 (295.0)	161 (261.9)	205 (161.6)
Serious AE(s) or related discontinuations						
Death	2 (0.6)	0 (0.0)	1 (0.5)	2 (1.3)	0 (0.0)	0 (0.0)
Non-fatal SAE(s)	59 (16.7)	12 (15.2)	32 (14.6)	25 (16.4)	2 (3.3)	14 (11.0)
Non-fatal SAE(s) leading to discontinuation	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	3 (2.4)
Non-serious AE(s) leading to discontinuation	2 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	2 (1.6)

(1) 1st treatment/re-treatment with ACZ; n = Number of events.
The incidence rate per 100 patient-years (IR/100 pyr) is 100 times (total number of occurrence of events divided by patient-years). It is calculated per category. Patient-years is the total time at risk in years. It is the sum of all patient's times at risk, i.e. duration of exposure until the date of last study day.

Other Relevant Findings

None

Conclusion:

In this third extension study, no new long-term safety signals were observed after re-treatment with canakinumab. Canakinumab reduced the overall flare, and efficacy of canakinumab upon re-treatment was maintained long-term.

Date of Clinical Trial Report

30 April 2014