Sponsor

Novartis

Generic Drug Name

Canakinumab

Therapeutic Area of Trial

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. Novartis is currently Marketing Authorization Holder in 69 countries worldwide for the 150 mg powder for solution for injection and in 25 countries worldwide for the 150 mg powder and solvent for injection (convenient kit).

Approval was obtained in the EU on 24 Jan 2013 for the application to extend the treatment in CAPS to children aged two years and older as well as to increase the maximum dose up to 600 mg or 8 mg/kg every 8 weeks in patients who do not achieve a satisfactory clinical response at the currently approved dose. This label extension was also approved in Russia, Philippines and Argentina.

Canakinumab also is approved for the treatment of acute gouty arthritis (GA) attacks in the Philippines Russia, Ecuador, Argentina, Israel, and Mexico. Approval was obtained in EU for the indication of "symptomatic treatment of acute gouty arthritis in patients with frequent attacks (≥ 3 in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDS) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate."

Canakinumab has also been approved for the treatment of systemic juvenile idiopathic arthritis (SJIA) in the Philippines, Russia and the United States. Submissions are either pending or are in progress worldwide.

Protocol Number

CACZ885H2361E1

Title

A 36-week open-label extension study of CACZ885H2361 on the safety and tolerability of canakinumab 150 mg s.c. pre-filled syringe (PFS) in treating acute gouty arthritis flares in frequently flaring patients

Study Phase

Phase III

Study Start/End Dates

25-Aug-2011 (first patient first visit) to 09-May-2013 (last patient last visit)

Study Design/Methodology

This was a 36-week, multi-center, open-label clinical extension study in patients with acute gouty arthritis flares. Patients completing the core study CACZ885H2361 were allowed to continue to be treated in this extension study for any new gouty arthritis flare on-demand. All enrolled patients were to receive canakinumab 150 mg s.c. PFS on-demand upon each new gouty arthritis flare regardless of their treatment in the core study.

Centers

Total of 68 centers in this extension study: Canada (3), Germany (5), Lithuania (6), United States (54).

Objectives

The primary objective of this study was to evaluate the long-term safety, tolerability and immunogenicity of canakinumab 150 mg s.c. administered as PFS.

Secondary objectives included 1) to evaluate the time to first new gouty arthritis flare since initial dose in core study; 2) to evaluate the frequency of new gouty arthritis flares; 3) to evaluate the long-term efficacy of canakinumab 150 mg s.c. PFS with respect to the treatment of signs and symptoms of new gouty arthritis flares (pain intensity using Likert and VAS scale, patient's and physician's global assessment of response to treatment, and physician's assessment of tenderness, swelling and erythema of the most affected joint); and 4) to evaluate the pharmacokinetics (PK) of canakinumab 150 mg s.c. PFS.

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

All patients were to receive canakinumab 150 mg (PFS) s.c., given on demand upon new flares. Canakinumab (PFS for s.c. injection were supplied to the investigators at dose strengths of 1 mL solution (150 mg).

Statistical Methods

The data analysis was a follow-up analysis from the core study and the analysis included all data from the core and extension studies.

For demographic and baseline characteristics (from the core study), summary statistics were provided by treatment group. Relevant medical history/current medical conditions were listed and summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. The number and percentage of patients taking concomitant medication and non-drug therapies were summarized by ATC class and treatment group.

The safety set was used for the analysis of safety data during the core and extension studies. Adverse events (AE) were summarized by presenting, for each treatment group, the number and percentage of patients having any AE based on the preferred term. All other information collected (e.g. severity, relationship to study drug) was tabulated and listed as appropriate. In addition, AE incidence rate adjusted by duration of exposure in patient years was presented. Deaths, SAEs, and AEs leading to discontinuation of study drug were summarized by primary SOC and PT and listings were provided.

All efficacy analyses were performed using the FAS or the MAS. All variables were analyzed using two-sided tests at a 0.05 significance level. Time to first new gouty arthritis flare was tested for the superiority of canakinumab (PFS) to triamcinolone acetonide using the FAS.

Treatment difference for time to first new gouty arthritis flare was analyzed using a Cox proportional hazard regression model with treatment, Uric acid Lowering Therapy (ULT) use and BMI at baseline as explanatory variables using FAS. The Kaplan-Meier estimates of the proportion of patients with first new gout flare, along with the associated 95% confidence intervals using the Greenwood's formula were provided. The first new flare could have occurred in core or extension of the study right prior to the switch.

Pain values (VAS) and patient's assessment of gout pain intensity in the most affected joint at baseline (Likert scale), physician's assessment of tenderness, swelling, erythema of the most affected joint (Likert scale) and patient's and physician's global assessment of response to treatment (Likert scale) were summarized at scheduled study visits for baseline flare and the 1st, 2nd, and the last post-baseline flares treated with canakinumab (PFS) by time point using the MAS.

The number of flares per patient was analyzed using a negative binomial generalized linear model with ULT use and BMI at baseline as explanatory variables. This analysis was performed using the FAS. The flares occurred in the extension were only considered until the 1st dosed flare in the extension study (including this flare). The flares occurred after switching to the PFS in extension study were not considered.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients, who completed the core study CACZ885H2361 up to and including the End of Study visit (Visit 8) having fulfilled the entry criteria, were eligible for this extension study.

Patients were excluded from this extension study if their entry was considered inappropriate by the treating physician.

Participant Flow

Patient disposition (Randomized Set)

Disposition Reason	ACZ885 150 mg s.c. (PFS) (N=133) All ACZ (PFS) N=133 n (%)	ACZ885 150 mg s.c. (PFS) (N=133) Re-treated with ACZ (PFS) N=57 n (%)	ACZ885 150 mg s.c. (LYO) (N=132) All ACZ (LYO) N=132 n (%)	ACZ885 150 mg s.c. (LYO) (N=132) Treated with ACZ (PFS) N=49 n (%)	Triam 40 mg i.m. (N=132) All Triam N=132 n (%)	Triam 40 mg i.m. (N=132) Treated with ACZ (PFS) N=50 n (%)	Total N=397 n (%)
Completed core study	124 (93.2)	57 (100.0)	117 (88.6)	49 (100.0)	108 (81.8)	50 (100.0)	349 (87.9)
Discontinued core study	9 (6.8)	0 (0.0)	15 (11.4)	0 (0.0)	24 (18.2)	0 (0.0)	48 (12.1)
Entered extension 1 study	85 (63.9)	55 (96.5)	71 (53.8)	49 (100.0)	76 (57.6)	50 (100.0)	232 (58.4)
Completed extension 1 study	67 (50.4)	43 (75.4)	61 (46.2)	45 (91.8)	70 (53.0)	46 (92.0)	198 (49.9)
Discontinued extension 1 study	18 (13.5)	12 (21.1)	10 (7.6)	4 (8.2)	6 (4.5)	4 (8.0)	34 (8.6)
Discontinued core or extension 1	27 (20.3)	12 (21.1)	25 (18.9)	4 (8.2)	30 (22.7)	4 (8.0)	82 (20.7)
Reason for discontinuation in core or extension 1							
Adverse event(s)	1 (0.8)	0 (0.0)	3 (2.3)	1 (2.0)	1 (0.8)	0 (0.0)	5 (1.3)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	2 (1.5)	2 (3.5)	2 (1.5)	1 (2.0)	4 (3.0)	0 (0.0)	8 (2.0)
Patient´s condition no longer requires study drug	0 (0.0)	0 (0.0)	1 (0.8)	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.3)
Patient withdrew consent	14 (10.5)	7 (12.3)	5 (3.8)	0 (0.0)	8 (6.1)	0 (0.0)	27 (6.8)
Lost to follow-up	7 (5.3)	2 (3.5)	9 (6.8)	1 (2.0)	7 (5.3)	1 (2.0)	23 (5.8)
Administrative problems	1 (0.8)	0 (0.0)	4 (3.0)	0 (0.0)	6 (4.5)	1 (2.0)	11 (2.8)
Death	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Protocol deviation	1 (0.8)	1 (1.8)	1 (0.8)	0 (0.0)	4 (3.0)	2 (4.0)	6 (1.5)

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 40 mg i.m. and discontinued after switching to ACZ 150 mg s.c. (PFS), this discontinuation is shown in both “All Triam” and “Treated with ACZ (PFS)” columns. This is also applicable to the patients randomized to ACZ (LYO) group.

Two Patients were mis-randomized first and then re-randomized. So these patients were counted twice.

Analysis sets by treatment (Randomized Set)

	ACZ885 150 mg s.c. (PFS) (N=133)		ACZ885 150 mg s.c. (LYO) (N=132)		Triam 40 mg i.m. (N=132)		
	All ACZ N=133 n (%)	Re-treated with ACZ (PFS) N=57 n (%)	All LYO N=132 n (%)	Treated with ACZ (PFS) N=49 n (%)	All Triam N=132 n (%)	Treated with ACZ (PFS) N=50 n (%)	Total N=397 n (%)
Randomized Set	133 (100.0)	57 (100.0)	132 (100.0)	49 (100.0)	132 (100.0)	50 (100.0)	397 (100.0)
Full Analysis Set	131 (98.5)	57 (100.0)	129 (97.7)	49 (100.0)	129 (97.7)	50 (100.0)	389 (98.0)
Modified Analysis Set	131 (98.5)	57 (100.0)	129 (97.7)	49 (100.0)	129 (97.7)	50 (100.0)	389 (98.0)
Safety Set	133 (100.0)	58 (101.8)	133 (100.8)	51 (104.1)	133 (100.8)	51 (102.0)	389 (98.0)

Safety Set: 1). The patients with more than one treatment are counted in the Safety Set under those treatment groups as the actual treatments they received. But these patients are counted only once in the "Total" column. Therefore the percentages for the Safety Set row which are based on the "N" values in the column header may exceed 100%.

2). The patients with "No active treatment" are counted in Safety Set row only in the "Total" column. By default these patients are counted in the Randomized Set and FAS as per their randomized group.

Baseline Characteristics

Demographic and background characteristics by treatment (Safety Set)

	ACZ885 150 mg s.c. (PFS) (N=133)		ACZ885 150 mg s.c. (LYO) (N=133)		Triam 40 mg i.m. (N=133)		
Demographic variable	All ACZ (PFS) N=133	Re-treated with ACZ (PFS) N=58	All ACZ (LYO) N=133	Treated with ACZ (PFS) N=51	All Triam N=133	Treated with ACZ (PFS) N=51	Total N=388
Sex							
Male	118 (88.7%)	54 (93.1%)	124 (93.2%)	51 (100.0%)	122 (91.7%)	47 (92.2%)	354 (91.2%)
Female	15 (11.3%)	4 (6.9%)	9 (6.8%)	0 (0.0%)	11 (8.3%)	4 (7.8%)	34 (8.8%)
Age (years)							
n	133	58	133	51	133	51	388
Mean	53.4	52.9	53.0	52.5	53.7	53.7	53.5
SD	11.21	12.20	11.84	10.86	11.33	12.30	11.44
Median	54.0	52.5	52.0	51.0	53.0	52.0	53.0
Min	24	27	25	31	23	26	23
Max	84	80	83	75	85	79	85
Age groups							
< 65 years	113 (85.0%)	47 (81.0%)	105 (78.9%)	40 (78.4%)	110 (82.7%)	41 (80.4%)	318 (82.0%)
>= 65-74 years	15 (11.3%)	9 (15.5%)	24 (18.0%)	10 (19.6%)	18 (13.5%)	7 (13.7%)	56 (14.4%)
>= 75 years	5 (3.8%)	2 (3.4%)	4 (3.0%)	1 (2.0%)	5 (3.8%)	3 (5.9%)	14 (3.6%)
Race							
Caucasian	93 (69.9%)	40 (69.0%)	94 (70.7%)	31 (60.8%)	98 (73.7%)	38 (74.5%)	279 (71.9%)

Demographic variable	ACZ885 150 mg s.c. (PFS) (N=133) All ACZ (PFS) N=133	ACZ885 150 mg s.c. (PFS) (N=133) Re-treated with ACZ (PFS) N=58	ACZ885 150 mg s.c. (LYO) (N=133) All ACZ (LYO) N=133	ACZ885 150 mg s.c. (LYO) (N=133) Treated with ACZ (PFS) N=51	Triam 40 mg i.m. (N=133) All Triam N=133	Triam 40 mg i.m. (N=133) Treated with ACZ (PFS) N=51	Total N=388
Black	35 (26.3%)	16 (27.6%)	31 (23.3%)	17 (33.3%)	29 (21.8%)	13 (25.5%)	90 (23.2%)
Asian	4 (3.0%)	1 (1.7%)	4 (3.0%)	2 (3.9%)	4 (3.0%)	0 (0.0%)	12 (3.1%)
Native American	0 (0.0%)	0 (0.0%)	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%)	0 (0.0%)	0 (0.0%)
Other	1 (0.8%)	1 (1.7%)	4 (3.0%)	1 (2.0%)	2 (1.5%)	0 (0.0%)	7 (1.8%)
BMI (kg/m^2)							
n	133	58	133	51	133	51	388
Mean	31.89	31.75	31.94	32.66	32.16	32.01	32.00
SD	4.873	5.030	5.037	4.900	5.300	5.202	5.059
Median	31.49	31.36	31.39	32.11	31.51	31.05	31.49
Min	21.2	21.2	20.3	24.3	20.5	21.2	20.3
Max	44.4	44.4	44.9	44.8	44.3	42.4	44.9

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

Outcome Measures

Primary Outcome Result(s)

As the primary objective of this extension study was to evaluate the long-term safety, tolerability and immunogenicity of canakinumab 150 mg s.c. administered as PFS, there is no primary efficacy variable. All efficacy variables are part of the secondary objectives of the study.

Secondary Outcome Result(s)

Time to first new flare: Survival analysis by treatment (Full Analysis Set)

	Kaplan-Meier estimate			Cox's proportional hazard regression model			
Treatment	N	End of study (%)	95% CI	N	Hazard ratio PFS to LYO or Triam	95% CI	Two-sided p-value
Canakinumab 150 mg s.c. (PFS)	131	65.50	(54.97, 75.81)	131	NA	NA	NA
Canakinumab 150 mg s.c. (LYO)	129	75.42	(63.82, 85.57)	129	0.89	(0.61, 1.29)	0.5279
Triam 40 mg i.m.	129	72.95	(62.95, 82.12)	129	0.45	(0.32, 0.64)	<0.0001*

Cox's proportional hazard regression model with treatment group, ULT use and BMI at baseline as covariates.
* denotes a p-value <=0.05; CI = confidence interval

Flare rate per year: Rate ratio estimate of treatment effect from negative binomial model (Full Analysis Set)

			Rate (flares/year)		Rate ratio PFS to LYO or Triam		
	N	Mean flare rate per year	Estimate	95% CI	Estimate	95% CI	Two-sided p-value
Canakinumab 150 mg s.c. (PFS)	131	0.95	1.11	(0.88, 1.40)	NA	NA	NA
Canakinumab 150 mg s.c. (LYO)	129	1.13	1.09	(0.83, 1.44)	1.01	(0.70, 1.46)	0.9383
Triam 40 mg i.m.	129	2.90	2.51	(2.01, 3.15)	0.44	(0.32, 0.61)	<0.0001*

Rate ratio ACZ885 150 mg s.c. (PFS)/ Triam 40 mg i.m. or ACZ885 150 mg s.c. (PFS)/ ACZ885 150 mg s.c. (LYO) is estimated from negative binomial model with treatment group, ULT use and BMI at baseline as covariates and log(time on study) as an offset.

* denotes a p-value <=0. 05. CI = confidence interval

Post-baseline flares compared to baseline flare: VAS pain in patients who were re-treated with canakinumab PFS (Modified Analysis Set)

	Canakinumab 150 mg s.c. PFS re-treated with canakinumab PFS N=57	
Assessment / Timepoint	**Baseline flare**	**Last new flare**
Pain intensity (VAS): ≥75% change from baseline		
6 hours post-dose	5/48 (10.4%)	2/48 (4.2%)
12 hours post-dose	9/49 (18.4%)	9/49 (18.4%)
24 hours post-dose	22/47 (46.8%)	16/47 (34.0%)
48 hours post-dose	27/47 (57.4%)	23/47 (48.9%)
72 hours post-dose	35/52 (67.3%)	37/52 (71.2%)
4 days post-dose	35/46 (76.1%)	32/46 (69.6%)
5 days post-dose	37/47 (78.7%)	36/47 (76.6%)
6 days post-dose	33/42 (78.6%)	33/42 (78.6%)
7 days post-dose	41/48 (85.4%)	42/48 (87.5%)
8 days post-dose	35/38 (92.1%)	30/38 (78.9%)
9 days post-dose	32/36 (88.9%)	32/36 (88.9%)
10 days post-dose	32/36 (88.9%)	30/36 (83.3%)
11 days post-dose	33/36 (91.7%)	31/36 (86.1%)
12 days post-dose	30/34 (88.2%)	29/34 (85.3%)
13 days post-dose	31/33 (93.9%)	28/33 (84.8%)
14 days post-dose	29/32 (90.6%)	28/32 (87.5%)

At each time point, only patients with a value at both baseline flare and the last post-baseline flare were included.

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

	Canakinumab 150 mg s.c. PFS re-treated with canakinumab PFS N=57	
Assessment / Timepoint	**Baseline flare**	**Last new flare**
Pain intensity (Likert scale): None or Mild		
Baseline	1/56 (1.8%)	1/56 (1.8%)
6 hours post-dose	12/49 (24.5%)	11/49 (22.4%)
12 hours post-dose	19/50 (38.0%)	20/50 (40.0%)
24 hours post-dose	31/48 (64.6%)	29/48 (60.8%)
48 hours post-dose	37/48 (77.1%)	35/48 (72.9%)
72 hours post-dose	45/53 (84.9%)	46/53 (86.8%)
4 days post-dose	43/47 (91.5%)	40/47 (85.1%)
5 days post-dose	42/48 (87.5%)	45/48 (93.7%)
6 days post-dose	39/44 (88.6%)	41/44 (93.1%)
7 days post-dose	48/49 (98.0%)	48/49 (98.0%)
8 days post-dose	37/39 (94.9%)	37/39 (94.9%)
9 days post-dose	37/37 (100.0%)	36/37 (97.3%)
10 days post-dose	36/37 (97.3%)	37/37 (100.0%)
11 days post-dose	37/37 (100.0%)	33/37 (89.2%)
12 days post-dose	33/35 (94.3%)	33/35 (94.3%)
13 days post-dose	32/34 (94.1%)	33/34 (97.1%)
14 days post-dose	33/34 (97.1%)	32/34 (94.1%)
Patient's global assessment of response to treatment: Excellent or Good		
72 hours post-dose	41/51 (80.4%)	38/51 (74.5%)
7 days post-dose	45/51 (88.3%)	48/51 (94.1%)
Physician's global assessment of response to treatment: Very good or Good		
72 hours post-dose	43/53 (81.1%)	42/53 (79.2%)
7 days post-dose	50/52 (96.2%)	47/52 (90.4%)
Physician's assessment of joint tenderness: No pain		
Baseline	0/56 (0.0%)	0/56 (0.0%)
72 hours post-dose	26/53 (49.1%)	28/53 (52.8%)
7 days post-dose	39/52 (75.0%)	41/52 (78.8%)
Physician's assessment of joint swelling: No swelling		
Baseline	0/56 (0.0%)	2/56 (3.6%)
72 hours post-dose	34/53 (64.2%)	33/53 (62.3%)
7 days post-dose	43/52 (82.7%)	42/52 (80.8%)
Physician's assessment of erythema: Absent		
Baseline	9/52 (17.3%)	13/52 (25.0%)
72 hours post-dose	48/51 (94.1%)	42/51 (82.4%)
7 days post-dose	46/50 (92.0%)	49/50 (98.0%)

	Canakinumab 150 mg s.c. PFS re-treated with canakinumab PFS N=57	
Assessment / Timepoint	**Baseline flare**	**Last new flare**
At each timepoint only patients with a value at both baseline flare and the last post-baseline flare were included.		

Post-baseline flares compared to baseline flare: VAS pain in patients switching treatment from canakinumab (LYO) or triamcinolone acetonide to canakinumab (PFS) (Modified analysis set)

	Randomized to canakinumab 150 mg s.c. (LYO) and switched to canakinumab (PFS) N=49		Randomized to Triam 40 mg i.m. and switched to canakinumab (PFS) N=50	
Assessment / Timepoint	**Baseline flare on canakinumab (LYO)**	**First new flare on canakinumab (PFS)**	**Baseline flare on Triam**	**First new flare on canakinumab (PFS)**
Pain intensity (VAS): ≥75% change from baseline				
6 hours post-dose	4/44 (9.1%)	1/44 (2.3%)	6/45 (13.3%)	0/45 (0.0%)
12 hours post-dose	7/43 (16.3%)	7/43 (16.3%)	6/43 (14.0%)	4/43 (9.3%)
24 hours post-dose	8/39 (20.5%)	9/39 (23.1%)	13/38 (34.2%)	13/38 (34.2%)
48 hours post-dose	19/42 (45.2%)	19/42 (45.2%)	18/43 (41.9%)	27/43 (62.8%)
72 hours post-dose	21/40 (52.5%)	22/40 (55.0%)	22/48 (45.8%)	35/48 (72.9%)
4 days post-dose	28/43 (65.1%)	26/43 (60.5%)	17/40 (42.5%)	32/40 (80.0%)
5 days post-dose	33/43 (76.7%)	30/43 (69.8%)	21/39 (53.8%)	34/39 (87.2%)
6 days post-dose	28/39 (71.8%)	30/39 (76.9%)	22/37 (59.5%)	32/37 (86.5%)
7 days post-dose	32/41 (78.0%)	33/41 (80.5%)	33/45 (73.3%)	42/45 (93.3%)
8 days post-dose	26/32 (81.3%)	27/32 (84.4%)	24/33 (72.7%)	31/33 (93.9%)
9 days post-dose	26/31 (83.9%)	26/31 (83.9%)	23/31 (74.2%)	30/31 (96.8%)
10 days post-dose	24/29 (82.8%)	25/29 (86.2%)	21/28 (75.0%)	26/28 (92.9%)
11 days post-dose	23/28 (82.1%)	24/28 (85.7%)	21/29 (72.4%)	29/29 (100.0%)
12 days post-dose	23/28 (82.1%)	26/28 (92.9%)	21/29 (72.4%)	29/29 (100.0%)
13 days post-dose	22/27 (81.5%)	24/27 (88.9%)	19/25 (76.0%)	25/25 (100.0%)
14 days post-dose	19/25 (76.0%)	22/25 (88.0%)	20/25 (80.0%)	23/25 (92.0%)

At each time point, only patients with a value at both baseline flare and the first post-baseline flare were included.

Post-baseline flares compared to baseline flare: clinical response in patients switching treatment from canakinumab (LYO) or triamcinolone acetonide to canakinumab (PFS) (Modified analysis set)

	Randomized to canakinumab 150 mg s.c. (LYO) and switched to canakinumab (PFS) N=49		Randomized to Triam 40 mg i.m. and switched to canakinumab (PFS) N=50	
Assessment / Timepoint	**Baseline flare on canakinumab (LYO)**	**First new flare on canakinumab (PFS)**	**Baseline flare on Triam**	**First new flare on canakinumab (PFS)**
Pain intensity (Likert scale): None or Mild				
Baseline	1/48 (2.1%)	4/48 (8.3%)	1/50 (2.0%)	2/50 (4.0%)
6 hours post-dose	9/45 (20.0%)	10/45 (22.2%)	13/45 (28.9%)	4/45 (8.9%)

Assessment / Timepoint	Randomized to canakinumab 150 mg s.c. (LYO) and switched to canakinumab (PFS) N=49		Randomized to Triam 40 mg i.m. and switched to canakinumab (PFS) N=50	
	Baseline flare on canakinumab (LYO)	First new flare on canakinumab (PFS)	Baseline flare on Triam	First new flare on canakinumab (PFS)
12 hours post-dose	14/44 (31.8%)	17/44 (38.6%)	18/43 (41.9%)	10/43 (23.3%)
24 hours post-dose	19/39 (48.7%)	22/39 (56.4%)	20/37 (54.1%)	21/37 (56.8%)
48 hours post-dose	28/43 (65.1%)	30/43 (69.8%)	26/43 (60.5%)	38/43 (88.4%)
72 hours post-dose	28/40 (70.0%)	29/40 (72.5%)	32/48 (66.7%)	44/48 (91.7%)
4 days post-dose	36/43 (83.7%)	36/43 (83.7%)	26/40 (65.0%)	39/40 (97.5%)
5 days post-dose	37/43 (86.0%)	38/43 (88.4%)	25/39 (64.1%)	38/39 (97.4%)
6 days post-dose	32/39 (82.1%)	35/39 (89.7%)	24/37 (64.9%)	37/37 (100%)
7 days post-dose	33/40 (82.5%)	36/40 (90.0%)	39/45 (86.7%)	45/45 (100%)
8 days post-dose	29/33 (87.9%)	31/33 (94.0%)	26/33 (78.8%)	33/33 (100.0%)
9 days post-dose	31/32 (96.9%)	30/32 (93.7%)	25/31 (80.6%)	31/31 (100.0%)
10 days post-dose	28/30 (93.3%)	29/30 (96.7%)	23/28 (82.2%)	28/28 (100.0%)
11 days post-dose	26/29 (89.6%)	28/29 (96.5%)	24/29 (82.7%)	29/29 (100.0%)
12 days post-dose	26/29 (89.6%)	28/29 (96.5%)	24/29 (82.7%)	29/29 (100.0%)
13 days post-dose	24/27 (88.9%)	26/27 (96.3%)	21/25 (84.0%)	25/25 (100.0%)
14 days post-dose	22/25 (88.0%)	23/25 (92.0%)	21/25 (84.0%)	25/25 (100.0%)
Patient's global assessment of response to treatment: Excellent or Good				
72 hours post-dose	26/39 (66.7%)	27/39 (69.2%)	25/45 (55.6%)	37/45 (82.2%)
7 days post-dose	35/42 (83.3%)	38/42 (90.5%)	35/46 (76.1%)	43/46 (93.5%)
Physician's global assessment of response to treatment: Very good or Good				
72 hours post-dose	35/40 (87.5%)	35/40 (87.5%)	27/47 (57.4%)	44/47 (93.6%)
7 days post-dose	44/49 (89.8%)	47/49 (95.9%)	35/49 (71.4%)	46/49 (93.9%)
Physician's assessment of joint tenderness: No pain				
Baseline	0/49 (0.0%)	1/49 (2.0%)	0/50 (0.0%)	0/50 (0.0%)
72 hours post-dose	14/40 (35.0%)	19/40 (47.5%)	13/47 (27.7%)	27/47 (57.4%)
7 days post-dose	36/49 (73.5%)	40/49 (81.6%)	27/49 (55.1%)	41/49 (83.7%)
Physician's assessment of joint swelling: No swelling				
Baseline	2/49 (4.1%)	1/49 (2.0%)	4/50 (8.0%)	3/50 (6.0%)
72 hours post-dose	24/40 (60.0%)	22/40 (55.0%)	24/47 (51.1%)	30/47 (63.8%)
7 days post-dose	42/49 (85.7%)	44/49 (89.8%)	38/49 (77.6%)	45/49 (91.8%)
Physician's assessment of erythema: Absent				
Baseline	13/48 (27.1%)	16/48 (33.3%)	15/50 (30.0%)	18/50 (36.0%)
72 hours post-dose	35/39 (89.7%)	33/39 (84.6%)	34/46 (73.9%)	39/46 (84.8%)
7 days post-dose	47/49 (95.9%)	48/49 (98.0%)	44/49 (89.8%)	49/49 (100.0%)

At each time point, only patients with a value at both baseline flare and the first post-baseline flare were included. For Triam 40 mg i.m. patients treated with canakinumab the baseline flare was treated with Triam 40 mg i.m. and the 1st new flare was treated with canakinumab 150 mg s.c. (PFS). This was also applicable to patients randomized to canakinumab (LYO).

Safety Results

Exposure adjusted (per 100 patient years) incidence of frequent AEs (incidence rate per 100 patient years greater than 5 in any treatment group) by primary system organ class (safety set)

	ACZ885 150mg s.c. (PFS) (N=133)			ACZ885 150mg s.c. (LYO) (N=133)			Triam 40mg i.m. (N=133)		
		Re-treated with ACZ (PFS) (N=58)			Treated with ACZ (PFS) (N=51)			Treated with ACZ (PFS) (N=51)	
	All ACZ (PFS) N=133 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All ACZ (LYO) N=133 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All Triam N=133 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)
Total	225 (254.9)	68 (247.2)	75 (320.6)	140 (224.8)	67 (229.2)	42 (239.0)	211 (362.7)	70 (319.7)	53 (218.9)
Investigations	48 (54.4)	13(47.3)	24 (102.6)	19 (30.5)	9 (30.8)	3 (17.1)	44 (75.6)	14(63.9)	8 (33.0)
Infections and infestations	34 (38.5)	11(40.0)	13(55.6)	35 (56.2)	18(61.6)	3 (17.1)	20 (34.4)	8 (36.5)	9 (37.2)
Musculoskeletal and connective tissue disorders	30 (34.0)	12(43.6)	4 (17.1)	24 (38.5)	10(34.2)	8 (45.5)	22 (37.8)	8 (36.5)	7 (28.9)
Metabolism and nutrition disorders	13 (14.7)	6 (21.8)	4 (17.1)	8 (12.8)	5 (17.1)	5 (28.5)	15 (25.8)	7 (32.0)	5 (20.7)
Gastrointestinal disorders	19 (21.5)	4 (14.5)	6 (25.6)	4 (6.4)	2 (6.8)	5 (28.5)	12 (20.6)	3 (13.7)	2 (8.3)
Nervous system disorders	12 (13.6)	4 (14.5)	6 (25.6)	2 (3.2)	0	2 (11.4)	13 (22.3)	5 (22.8)	1 (4.1)
Respiratory, thoracic and mediastinal disorders	8 (9.1)	2 (7.3)	2 (8.5)	8 (12.8)	2 (6.8)	2 (11.4)	11 (18.9)	3 (13.7)	4 (16.5)
Cardiac disorders	3 (3.4)	1 (3.6)	0	10 (16.1)	6 (20.5)	1 (5.7)	12 (20.6)	3 (13.7)	0
Vascular disorders	7 (7.9)	4 (14.5)	1 (4.3)	7 (11.2)	5 (17.1)	3 (17.1)	11 (18.9)	4 (18.3)	2 (8.3)
Renal and urinary disorders	10 (11.3)	1 (3.6)	6 (25.6)	2 (3.2)	0	3 (17.1)	11 (18.9)	1 (4.6)	4 (16.5)
Skin and subcutaneous tissue disorders	6 (6.8)	2 (7.3)	1 (4.3)	8 (12.8)	4 (13.7)	2 (11.4)	9 (15.5)	5 (22.8)	1 (4.1)
General disorders and administration site conditions	11 (12.5)	1 (3.6)	2 (8.5)	1 (1.6)	1 (3.4)	2 (11.4)	10 (17.2)	4 (18.3)	1 (4.1)
Injury, poisoning and procedural complications	12 (13.6)	3 (10.9)	4 (17.1)	4 (6.4)	3 (10.3)	3 (17.1)	4 (6.9)	3 (13.7)	3 (12.4)
Blood and lymphatic system disorders	2 (2.3)	1 (3.6)	0	4 (6.4)	1 (3.4)	0	4 (6.9)	0	2 (8.3)
Psychiatric disorders	3 (3.4)	1 (3.6)	0	0	0	0	4 (6.9)	1 (4.6)	1 (4.1)

Primary system organ classes are sorted by descending frequency of the total number observed for all patients.

n = Number of events, IR = incidence rate

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 (PFS).

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

	ACZ885 150mg s.c. (PFS)(N=133)			ACZ885 150mg s.c. (LYO)(N=133)			Triam 40mg i.m. (N=133)		
		Re-treated with ACZ (PFS) (N=58)			Treated with ACZ (PFS) (N=51)			Treated with ACZ (PFS) (N=51)	
	All ACZ (PFS) N=133 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All ACZ (LYO) N=133 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All Triam N=133 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)
Any AE(s)	225 (254.9)	68 (247.2)	75 (320.6)	140 (224.8)	67 (229.2)	42 (239.0)	211 (362.7)	70 (319.7)	53 (218.9)
Serious AE(s) or related discontinuations									
Death	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAE(s)	12 (13.6)	3 (10.9)	5 (21.4)	10 (16.1)	4 (13.7)	3 (17.1)	9 (15.5)	0 (0.0)	1 (4.1)
Non-fatal SAE(s) leading to discontinuation	1 (1.1)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-serious AE(s) leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.7)	2 (3.4)	0 (0.0)	0 (0.0)

n = Number of events, IR = incidence rate

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 are the total time at risk in years. It is the sum of all patients' times at risk, i.e. duration of exposure until the date of last study day.

(1) 1st treatment/re-treatment with ACZ (PFS).

Other Relevant Findings

None

Date of Clinical Trial Report

29 April 2014

Date Inclusion on Novartis Clinical Trial Results Database

5 May 2014