Sponsor

Novartis

Generic Drug Name

Canakinumab (ACZ885)

Trial Indication(s)

Acute Gouty Arthritis

Protocol Number

CACZ885H2361E1

Protocol 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

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

25-Aug-2011 to 09-May-2013

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 milligrams (mg) subcutaneously (s.c.) PFS on-demand upon each new gouty arthritis flare regardless of their treatment in the core study.

Centers

68 centers in 4 countries: Canada (3), Germany (5), Lithuania (6), United States (54).

Objectives:

Primary objective

To evaluate the long-term safety, tolerability and immunogenicity of canakinumab 150 mg s.c. administered as PFS.

Secondary objective

- To evaluate the time to first new gouty arthritis flare since initial dose in core study.
- To evaluate the frequency of new gouty arthritis flares
- 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, defined as:
    - Patient's assessment of acute gouty arthritis pain intensity in the most affected joint (Likert scale) over time
    - Patient's assessment of acute gouty arthritis pain intensity in the most affected joint (on a 0-100 mm visual analogue scale [VAS]) over time
    - Patient's global assessment of response to treatment (Likert scale) over time
    - Physician's assessment of tenderness, swelling and erythema of the most affected joint over time
    - Physician's global assessment of response to treatment (Likert scale) over time
- To evaluate the pharmacokinetics (PK) of canakinumab 150 mg s.c. PFS

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

ACZ885 (canakinumab) 150 mg for s.c. injection.
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).

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

Not applicable.

Criteria for Evaluation

Primary variable:

Analysis of safety and tolerability data was presented according to the most recent treatment received in the core study CACZ885H2361:

- Canakinumab 150 mg s.c. Lyophilized (LYO)
- Canakinumab 150 mg s.c. pre-filled syringe (PFS)
- Triamcinolone acetonide 40 mg intramuscular (i.m.)

Secondary variable:

Long-term efficacy of canakinumab 150 mg s.c. PFS with respect to the treatment of signs and symptoms of new gout flares, defined as:

- Time to first new gouty arthritis flare
- Frequency of new gout flares
- Patient's assessment of acute gouty arthritis pain intensity in the most affected joint (Likert scale) over time
- Patient's assessment of acute gouty arthritis pain intensity in the most affected joint (on a 0-100 mm VAS) over time
- Patient's global assessment of response to treatment (Likert scale) over time
- Physician's assessment of tenderness, swelling and erythema of the most affected joint over time
- Physician's global assessment of response to treatment (Likert scale) over time

Pharmacokinetics (PK)

- Canakinumab concentrations were assessed in serum.

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.

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 efficacy analyses were performed using the Full Analysis set (FAS) or the Modified Analysis Set (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) and body mass index at baseline using FAS.

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: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Compliance and completion of the canakinumab PFS core study
- Unchanged significant clinical medical history from entry into core study

Exclusion criteria

- Physician judgment of unsuitability for the study
- Pregnant or nursing women Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Patient disposition (Randomized Set)

Disposition Reason	ACZ885 150mg sc (PFS) (N=133) All ACZ (PFS) N=133 n (%)	ACZ885 150mg sc (PFS) (N=133) Re-treated with ACZ (PFS) N=57 n (%)	ACZ885 150mg sc (LYO) (N=132) All ACZ (LYO) N=132 n (%)	ACZ885 150mg sc (LYO) (N=132) Treated with ACZ (PFS) N=49 n (%)	Triam 40mg im (N=132) All Triam N=132 n (%)	Triam 40mg im (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							
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 40mg im and discontinued after switching to ACZ 150mg sc (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.
The Patients 0508-00011 and 0520-00001 were mis-randomized first and re-randomized as 0508-00012 and 0520-00005 respectively. So these patients were counted twice.

Baseline Characteristics

Demographic and background characteristics by treatment (Safety Set)

		Canakinumab, Pre-filled Syringes (PFS)	Canakinumab, Lyophilizate (LYO)	Triamcinolone Acetonide	Total
Overall Number of Participants		1 3 3	132	13 2	397
Age, Customized Measure Count of Type: Participants Unit of participants measure:	Number Analyzed	133 participants	132 participants	132 participants	397 participants
< 65 years		113 84.96%	104 78.79%	110 83.33%	327 82.37%
>= 65-74 years		15 11.28%	24 18.18%	18 13.64%	57 14.36%
>= 75 years		5 3.76%	4 3.03%	4 3.03%	13 3.27%
Sex: Female, Male Measure Count of Type: Participants Unit of participants measure:	Number Analyzed	133 participants	132 participants	132 participants	397 participants
	Female	15 11.28%	9 6.82%	10 7.58%	34 8.56%
	Male	118 88.72%	123 93.18%	122 92.42%	363 91.44%
Race/Ethnicity, Customized Measure Count of Type: Participants Unit of participants measure:	Number Analyzed	133 participants	132 participants	132 participants	397 participants
Caucasian		93 69.92%	93 70.45%	97 73.48%	283 71.28%
Black		35 26.32%	31 23.48%	29 21.97%	95 23.93%
Asian		4 3.01%	4 3.03%	4 3.03%	12 3.02%
Native american		0 0%	0 0%	0 0%	0 0%
Pacific islander		0 0%	0 0%	0 0%	0 0%
Other		1 0.75%	4 3.03%	2 1.52%	7 1.76%

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% Confidence Interval	N	Hazard ratio PFS to LYO or Triam	95% Confidence Interval	Two-sided p-value
ACZ885 150mg sc (PFS)	131	65.50	(54.97, 75.81)	131	NA	NA	NA
ACZ885 150mg sc (LYO)	129	75.42	(63.82, 85.57)	129	0.89	(0.61, 1.29)	0.5279
Triam 40mg im	129	72.95	(62.95, 82.12)	129	0.45	(0.32, 0.64)	<0.0001 *

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

		Mean flare rate per year	Rate (flares/year)		Rate ratio PFS to LYO or Triam		Two-sided p-value
	N		Estimate	95% CI	Estimate	95% CI	
ACZ885 150mg sc (PFS)	131	0.95	1.11	(0.88, 1.40)	NA	NA	NA
ACZ885 150mg sc (LYO)	129	1.13	1.09	(0.83, 1.44)	1.01	(0.70, 1.46)	0.9383
Triam 40mg im	129	2.90	2.51	(2.01, 3.15)	0.44	(0.32, 0.61)	<0.0001 *

Number of Participant with New Flares

Statistic	ACZ885 150mg sc (PFS) N=131	ACZ885 150mg sc (LYO) N=129	Triam 40mg im N=129
n	131	129	129
Mean	0.76	0.50	0.96
SD	1.228	0.675	1.049
Min	0	0	0
Q1	0.00	0.00	0.00
Median	0.00	0.00	1.00
Q3	1.00	1.00	2.00
Max	8	4	4
Number of new flares - n (%)			
1	35 (26.7)	46 (35.7)	36 (27.9)
2	17 (13.0)	7 (5.4)	26 (20.2)
3	2 (1.5)	0 (0.0)	8 (6.2)
>3	4 (3.1)	1 (0.8)	3 (2.3)

New flares occurred before first study medication dose in extension 1 study were considered.

Change from baseline in Pain intensity (Likert scale): Last post-baseline flare treated with ACZ (PFS) (Modified Analysis Set)

Timepoint / Statistic	ACZ885 150mg sc (PFS) (N=131) Re-treated with ACZ (PFS) N=57	ACZ885 150mg sc (LYO) (N=129) Treated with ACZ (PFS) N=49	Triam 40mg im (N=129) Treated with ACZ (PFS) N=50
13 days post-dose			
n	45	32	35
Mean	-2.4	-2.4	-2.7
SD	0.92	1.01	0.66
Min	-4	-4	-4
Q1	-3.0	-3.0	-3.0
Median	-2.0	-2.5	-3.0
Q3	-2.0	-2.0	-2.0
Max	0	0	-1
14 days post-dose			
n	44	31	34
Mean	-2.5	-2.3	-2.8
SD	0.90	1.08	0.78
Min	-4	-4	-4
Q1	-3.0	-3.0	-3.0
Median	-2.0	-2.0	-3.0
Q3	-2.0	-2.0	-2.0
Max	0	0	0

Change from baseline = (post-baseline measurement - baseline).
Data for patients randomized to ACZ885 (LYO) are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS).
Data for patients randomized to Triam 40mg im are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS).

Change from baseline in Pain intensity (0–100mm VAS): Last post-baseline flare treated with ACZ (PFS) (Modified Analysis Set)

Timepoint / Statistic	ACZ885 150mg sc (PFS) (N=131) Re-treated with ACZ (PFS) N=57	ACZ885 150mg sc (LYO) (N=129) Treated with ACZ (PFS) N=49	Triam 40mg im (N=129) Treated with ACZ (PFS) N=50
6 hours post-dose			
n	51	47	46
Mean	-12.9	-13.0	-10.2
SD	21.03	17.14	15.78
Min	-79	-65	-56
Q1	-22.0	-21.0	-21.0
Median	-9.0	-10.0	-6.5
Q3	0.0	-1.0	1.0
Max	32	11	35
12 hours post-dose			
n	51	47	46
Mean	-23.7	-26.7	-23.4
SD	22.94	22.09	19.87
Min	-90	-72	-62
Q1	-35.0	-46.0	-41.0
Median	-18.0	-26.0	-24.5
Q3	-5.0	-8.0	-11.0
Max	18	18	21

24 hours post-dose			
n	52	46	46
Mean	-34.9	-36.1	-35.6
SD	24.88	24.55	27.09
Min	-88	-87	-90
Q1	-50.0	-49.0	-52.0
Median	-30.0	-36.5	-37.0
Q3	-20.0	-15.0	-22.0
Max	19	14	54
48 hours post-dose			
n	52	47	46
Mean	-46.4	-43.8	-51.1
SD	25.31	24.71	26.34
Min	-95	-88	-89
Q1	-60.0	-61.0	-72.0
Median	-49.0	-48.0	-54.5
Q3	-30.5	-28.0	-38.0
Max	13	6	20
72 hours post-dose			
n	53	42	47
Mean	-55.1	-45.8	-54.7
SD	26.97	28.74	30.41
Min	-100	-91	-99
Q1	-73.0	-72.0	-78.0
Median	-58.0	-49.0	-59.0
Q3	-37.0	-26.0	-38.0
Max	11	9	15
4 days post-dose			
n	51	46	44
Mean	-55.7	-50.0	-62.0
SD	26.91	26.39	23.86
Min	-100	-90	-100
Q1	-73.0	-72.0	-77.5
Median	-60.0	-52.5	-65.5
Q3	-38.0	-34.0	-46.0
Max	22	4	5

5 days post-dose			
n	51	46	42
Mean	-59.1	-54.3	-65.2
SD	25.99	25.43	23.78
Min	-100	-95	-100
Q1	-77.0	-75.0	-84.0
Median	-66.0	-57.0	-68.0
Q3	-49.0	-39.0	-52.0
Max	14	-3	0
6 days post-dose			
n	49	45	41
Mean	-61.2	-57.0	-66.0
SD	25.14	24.27	23.37
Min	-100	-98	-100
Q1	-77.0	-75.0	-85.0
Median	-66.0	-60.0	-68.0
Q3	-51.0	-42.0	-52.0
Max	9	0	3
7 days post-dose			
n	50	43	47
Mean	-62.1	-59.2	-66.6
SD	25.09	24.32	22.21
Min	-100	-98	-100
Q1	-79.0	-76.0	-85.0
Median	-67.0	-62.0	-68.0
Q3	-51.0	-50.0	-52.0
Max	4	2	0
8 days post-dose			
n	43	37	39
Mean	-59.9	-60.7	-66.8
SD	25.73	24.07	22.83
Min	-100	-98	-100
Q1	-76.0	-77.0	-85.0
Median	-67.0	-65.0	-67.0
Q3	-50.0	-51.0	-56.0
Max	12	6	-3

9 days post-dose			
n	42	37	35
Mean	-63.1	-61.1	-66.7
SD	23.93	24.34	23.21
Min	-100	-100	-100
Q1	-80.0	-78.0	-85.0
Median	-68.5	-65.0	-67.0
Q3	-51.0	-50.0	-52.0
Max	4	2	-3
10 days post-dose			
n	42	35	36
Mean	-63.0	-63.3	-67.9
SD	23.89	24.31	22.79
Min	-100	-100	-100
Q1	-77.0	-80.0	-88.0
Median	-68.5	-66.0	-67.5
Q3	-52.0	-53.0	-54.0
Max	5	5	-17
11 days post-dose			
n	43	35	36
Mean	-62.7	-64.3	-68.7
SD	25.19	23.53	22.04
Min	-100	-100	-100
Q1	-79.0	-78.0	-88.0
Median	-70.0	-69.0	-67.5
Q3	-51.0	-55.0	-57.0
Max	3	4	-21
12 days post-dose			
n	43	33	36
Mean	-63.3	-64.3	-69.4
SD	26.09	23.91	20.89
Min	-100	-100	-100
Q1	-80.0	-80.0	-88.0
Median	-70.0	-69.0	-68.0
Q3	-51.0	-55.0	-57.0
Max	2	2	-28

13 days post-dose			
n	42	33	36
Mean	-65.6	-64.0	-69.6
SD	23.25	24.47	20.67
Min	-100	-100	-100
Q1	-80.0	-79.0	-88.0
Median	-71.0	-69.0	-68.0
Q3	-52.0	-55.0	-57.0
Max	-2	7	-26
14 days post-dose			
n	41	32	35
Mean	-64.8	-64.8	-69.8
SD	24.66	24.15	21.25
Min	-100	-100	-100
Q1	-80.0	-81.0	-91.0
Median	-72.0	-70.5	-68.0
Q3	-52.0	-53.0	-57.0
Max	-2	-1	-30

Data for patients randomized to ACZ885 (LYO) are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS).
Data for patients randomized to Triam 40mg im are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS).

Patient's global assessment of response to treatment (Likert scale) over time: Last post-baseline flare treated with ACZ (PFS)

Timepoint / Assessment (Likert Scale)	ACZ885 150mg sc (PFS) (N=131)		ACZ885 150 mg sc (LYO) (N=129)	
	All ACZ (PFS) N=131	Re-treated with ACZ (PFS) N=57	All ACZ (LYO) N=129	Treated with ACZ (PFS) N=49
48 weeks post-dose				
Excellent	50 / 72 (69.4%)	32 / 46 (69.6%)	11 / 16 (68.8%)	0 / 0 (0.0%)
Good	17 / 72 (23.6%)	11 / 46 (23.9%)	4 / 16 (25.0%)	0 / 0 (0.0%)
Acceptable	2 / 72 (2.8%)	1 / 46 (2.2%)	1 / 16 (6.3%)	0 / 0 (0.0%)
Slight	3 / 72 (4.2%)	2 / 46 (4.3%)	0 / 16 (0.0%)	0 / 0 (0.0%)
Poor	0 / 72 (0.0%)	0 / 46 (0.0%)	0 / 16 (0.0%)	0 / 0 (0.0%)

Data for patients randomized to ACZ885 (LYO) are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS).
Data for patients randomized to Triam 40mg im are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS).

Change form baseline in Physician's assessment of tenderness, swelling and erythema

Parameter / Timepoint / Assessment	ACZ885 150mg sc (PFS) (N=131)		ACZ885 150 mg sc (LYO) (N=129)	
	All ACZ (PFS) N=131	Re-treated with ACZ (PFS) N=57	All ACZ (LYO) N=129	Treated with ACZ (PFS) N=49
Tenderness				
Baseline				
No pain	0 / 131 (0.0%)	0 / 57 (0.0%)	2 / 129 (1.6%)	0 / 49 (0.0%)
Pain	31 / 131 (23.7%)	14 / 57 (24.6%)	24 / 129 (18.6%)	6 / 49 (12.2%)
Pain and winces	41 / 131 (31.3%)	17 / 57 (29.8%)	54 / 129 (41.9%)	17 / 49 (34.7%)
Pain, winces and withdraws	59 / 131 (45.0%)	26 / 57 (45.6%)	49 / 129 (38.0%)	26 / 49 (53.1%)
72 hours post-dose				
No pain	65 / 130 (50.0%)	29 / 57 (50.9%)	50 / 125 (40.0%)	18 / 47 (38.3%)
Pain	56 / 130 (43.1%)	23 / 57 (40.4%)	66 / 125 (52.8%)	28 / 47 (59.6%)
Pain and winces	7 / 130 (5.4%)	4 / 57 (7.0%)	8 / 125 (6.4%)	1 / 47 (2.1%)
Pain, winces and withdraws	2 / 130 (1.5%)	1 / 57 (1.8%)	1 / 125 (0.8%)	0 / 47 (0.0%)
7 days post-dose				
No pain	96 / 125 (76.8%)	42 / 56 (75.0%)	89 / 125 (71.2%)	36 / 49 (73.5%)
Pain	29 / 125 (23.2%)	14 / 56 (25.0%)	35 / 125 (28.0%)	12 / 49 (24.5%)
Pain and winces	0 / 125 (0.0%)	0 / 56 (0.0%)	1 / 125 (0.8%)	1 / 49 (2.0%)
Pain, winces and withdraws	0 / 125 (0.0%)	0 / 56 (0.0%)	0 / 125 (0.0%)	0 / 49 (0.0%)

Parameter / Timepoint / Assessment	Triam 40mg im (N=129) All Triam N=129	Triam 40mg im (N=129) Treated with ACZ (PFS) N=50
Tenderness		
Baseline		
No pain	0 / 129 (0.0%)	0 / 50 (0.0%)
Pain	26 / 129 (20.2%)	14 / 50 (28.0%)
Pain and winces	49 / 129 (38.0%)	20 / 50 (40.0%)
Pain, winces and withdraws	54 / 129 (41.9%)	16 / 50 (32.0%)
72 hours post-dose		
No pain	36 / 121 (29.8%)	14 / 48 (29.2%)
Pain	57 / 121 (47.1%)	23 / 48 (47.9%)
Pain and winces	17 / 121 (14.0%)	6 / 48 (12.5%)
Pain, winces and withdraws	11 / 121 (9.1%)	5 / 48 (10.4%)
7 days post-dose		
No pain	70 / 123 (56.9%)	27 / 49 (55.1%)
Pain	41 / 123 (33.3%)	16 / 49 (32.7%)
Pain and winces	8 / 123 (6.5%)	5 / 49 (10.2%)
Pain, winces and withdraws	4 / 123 (3.3%)	1 / 49 (2.0%)

Parameter / Timepoint / Assessment	ACZ885 150mg sc (PFS) (N=131)		ACZ885 150 mg sc (LYO) (N=129)	
	All ACZ (PFS) N=131	Re-treated with ACZ (PFS) N=57	All ACZ (LYO) N=129	Treated with ACZ (PFS) N=49
Swelling				
Baseline				
No swelling	6 / 131 (4.6%)	1 / 57 (1.8%)	4 / 129 (3.1%)	2 / 49 (4.1%)
Palpable	24 / 131 (18.3%)	9 / 57 (15.8%)	20 / 129 (15.5%)	9 / 49 (18.4%)
Visible	72 / 131 (55.0%)	35 / 57 (61.4%)	63 / 129 (48.8%)	25 / 49 (51.0%)
Bulging beyond the joint margins	29 / 131 (22.1%)	12 / 57 (21.1%)	42 / 129 (32.6%)	13 / 49 (26.5%)
72 hours post-dose				
No swelling	79 / 130 (60.8%)	37 / 57 (64.9%)	69 / 125 (55.2%)	29 / 47 (61.7%)
Palpable	35 / 130 (26.9%)	16 / 57 (28.1%)	32 / 125 (25.6%)	11 / 47 (23.4%)
Visible	14 / 130 (10.8%)	4 / 57 (7.0%)	22 / 125 (17.6%)	6 / 47 (12.8%)
Bulging beyond the joint margins	2 / 130 (1.5%)	0 / 57 (0.0%)	2 / 125 (1.6%)	1 / 47 (2.1%)
7 days post-dose				
No swelling	104 / 125 (83.2%)	46 / 56 (82.1%)	105 / 125 (84.0%)	42 / 49 (85.7%)
Palpable	14 / 125 (11.2%)	8 / 56 (14.3%)	15 / 125 (12.0%)	4 / 49 (8.2%)
Visible	6 / 125 (4.8%)	2 / 56 (3.6%)	4 / 125 (3.2%)	2 / 49 (4.1%)
Bulging beyond the joint margins	1 / 125 (0.8%)	0 / 56 (0.0%)	1 / 125 (0.8%)	1 / 49 (2.0%)

Parameter / Timepoint / Assessment	Triam 40mg im (N=129) All Triam N=129	Triam 40mg im (N=129) Treated with ACZ (PFS) N=50
Swelling		
Baseline		
No swelling	7 / 129 (5.4%)	4 / 50 (8.0%)
Palpable	13 / 129 (10.1%)	4 / 50 (8.0%)
Visible	64 / 129 (49.6%)	27 / 50 (54.0%)
Bulging beyond the joint margins	45 / 129 (34.9%)	15 / 50 (30.0%)
72 hours post-dose		
No swelling	62 / 121 (51.2%)	25 / 48 (52.1%)
Palpable	19 / 121 (15.7%)	6 / 48 (12.5%)
Visible	30 / 121 (24.8%)	14 / 48 (29.2%)
Bulging beyond the joint margins	10 / 121 (8.3%)	3 / 48 (6.3%)
7 days post-dose		
No swelling	87 / 123 (70.7%)	38 / 49 (77.6%)
Palpable	18 / 123 (14.6%)	3 / 49 (6.1%)
Visible	16 / 123 (13.0%)	7 / 49 (14.3%)
Bulging beyond the joint margins	2 / 123 (1.6%)	1 / 49 (2.0%)

Parameter / Timepoint / Assessment	ACZ885 150mg sc (PFS) (N=131)		ACZ885 150 mg sc (LYO) (N=129)	
	All ACZ (PFS) N=131	Re-treated with ACZ (PFS) N=57	All ACZ (LYO) N=129	Treated with ACZ (PFS) N=49
Erythema				
Baseline				
Absent	22 / 128 (17.2%)	10 / 56 (17.9%)	34 / 128 (26.6%)	13 / 48 (27.1%)
Present	106 / 128 (82.8%)	46 / 56 (82.1%)	94 / 128 (73.4%)	35 / 48 (72.9%)
72 hours post-dose				
Absent	113 / 128 (88.3%)	53 / 56 (94.6%)	102 / 123 (82.9%)	42 / 46 (91.3%)
Present	15 / 128 (11.7%)	3 / 56 (5.4%)	21 / 123 (17.1%)	4 / 46 (8.7%)
7 days post-dose				
Absent	117 / 124 (94.4%)	51 / 55 (92.7%)	120 / 125 (96.0%)	47 / 49 (95.9%)
Present	7 / 124 (5.6%)	4 / 55 (7.3%)	5 / 125 (4.0%)	2 / 49 (4.1%)
4 weeks post-dose				
Absent	120 / 125 (96.0%)	52 / 55 (94.5%)	122 / 125 (97.6%)	47 / 49 (95.9%)
Present	5 / 125 (4.0%)	3 / 55 (5.5%)	3 / 125 (2.4%)	2 / 49 (4.1%)

Parameter / Timepoint / Assessment	Triam 40mg im (N=129) All Triam N=129	Triam 40mg im (N=129) Treated with ACZ (PFS) N=50
Erythema		
Baseline		
Absent	37 / 129 (28.7%)	15 / 50 (30.0%)
Present	92 / 129 (71.3%)	35 / 50 (70.0%)
72 hours post-dose		
Absent	81 / 118 (68.6%)	35 / 47 (74.5%)
Present	37 / 118 (31.4%)	12 / 47 (25.5%)
7 days post-dose		
Absent	110 / 123 (89.4%)	44 / 49 (89.8%)
Present	13 / 123 (10.6%)	5 / 49 (10.2%)
4 weeks post-dose		
Absent	105 / 112 (93.8%)	44 / 45 (97.8%)
Present	7 / 112 (6.3%)	1 / 45 (2.2%)

Data for patients randomized to ACZ885 (LYO) are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS). Data for patients randomized to Triam 40mg im are presented before the 1st treatment with ACZ (PFS) at scheduled study visits and after the 1st treatment with ACZ (PFS) at post-baseline flares treated with ACZ (PFS).

Change from baseline in Physician's global assessment of response to treatment

Timepoint / Assessment (Likert Scale)	ACZ885 150mg sc (PFS) (N=131) Re-treated with ACZ (PFS) N=57	ACZ885 150 mg sc (LYO) (N=129) Treated with ACZ (PFS) N=49	Triam 40mg im (N=129) Treated with ACZ (PFS) N=50
72 hours post-dose			
Very good	27 / 53 (50.9%)	21 / 43 (48.8%)	23 / 46 (50.0%)
Good	15 / 53 (28.3%)	17 / 43 (39.5%)	18 / 46 (39.1%)
Fair	9 / 53 (17.0%)	5 / 43 (11.6%)	3 / 46 (6.5%)
Poor	2 / 53 (3.8%)	0 / 43 (0.0%)	2 / 46 (4.3%)
Very poor	0 / 53 (0.0%)	0 / 43 (0.0%)	0 / 46 (0.0%)
7 days post-dose			
Very good	38 / 53 (71.7%)	33 / 49 (67.3%)	32 / 48 (66.7%)
Good	9 / 53 (17.0%)	14 / 49 (28.6%)	13 / 48 (27.1%)
Fair	5 / 53 (9.4%)	2 / 49 (4.1%)	2 / 48 (4.2%)
Poor	1 / 53 (1.9%)	0 / 49 (0.0%)	1 / 48 (2.1%)
Very poor	0 / 53 (0.0%)	0 / 49 (0.0%)	0 / 48 (0.0%)

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)

Other Relevant Findings

PK concentrations (ug/mL): Last post-baseline flare treated with ACZ (PFS) Summary statistics by timepoint and treatment (Safety Set)

Timepoint / statistic	ACZ885 150mg sc (PFS) (N=133) Retreated with ACZ (PFS) N=58	ACZ885 150mg sc (LYO) (N=133) Treated with ACZ (PFS) N=51
Baseline		
n	57	51
Mean	0.79	0.36
SD	1.423	0.930
CV% mean	180.85	260.67
Geo-mean	0.73	0.51
CV% geo-mean	227.38	192.03
Median	0.11	0
[Min; Max]	[0.0; 5.7]	[0.0; 4.9]
4 weeks post-dose		
n	55	45
Mean	6.46	5.78
SD	2.436	2.713
CV% mean	37.73	46.95
Geo-mean	6.11	5.20
CV% geo-mean	44.04	63.90
Median	6.73	5.39
[Min; Max]	[0.0; 12.2]	[0.0; 10.9]
12 weeks post-dose		
n	38	41
Mean	1.43	1.35
SD	0.800	1.080
CV% mean	56.01	80.27
Geo-mean	1.17	1.11
CV% geo-mean	95.46	80.80
Median	1.52	0.99
[Min; Max]	[0.0; 3.1]	[0.0; 5.3]

Conclusion:

This extension study provides further evidence that canakinumab (PFS) is effective in the treatment of signs and symptoms of gouty arthritis flares, with the additional benefit to the patients over triamcinolone acetonide in clinical response. In addition, the efficacy of canakinumab (PFS) was maintained upon re-treatment. There were no new safety signals and no indication of a worsening safety profile upon re-treatment with canakinumab. The overall benefit/risk of canakinumab in this indication remains positive and potentially better than that of triamcinolone acetonide.

Date of Clinical Study Report

03 April 2014