Sponsor

Novartis

Generic Drug Name

Canakinumab

Therapeutic Area of Trial

Gouty arthritis

Approved Indication

Indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children aged 4 years and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)/ Familial Cold Urticaria (FCU),
- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/ Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA).

Approved in 54 Countries: US, Switzerland, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, UK, Norway, Iceland, Chile, Guatemala, Canada, Brazil, Suriname, Argentina, Australia, Curacao, Hong Kong, Singapore, El Salvador, Israel, Taiwan, Philippines, India, UAE, Malaysia, Dominican Republic, Bahrain, Turkey, New Zealand, Kuwait, Peru.

Indicated for the treatment for gouty arthritis attacks.
Approved in the Philippines and the Russian Federation.

Study Numbers

CACZ885H2356, CACZ885H2356E1 and CACZ885H2356E2

Title

A 12 weeks randomized, controlled core study of ACZ885 (canakinumab) 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 including a 12 weeks extension study and an open-label 48 weeks extension study

Phase of Development

Phase III

Study Start/End Dates

CACZ885H2356	04-Dec-2009 to 26-Jul-2010 (core study)
CACZ885H2356E1	05-Mar-2010 to 12-Oct-2010 (first extension study)
CACZ885H2356E2	28-May-2010 to 27-Sep-2011 (second extension study)

Study Design/Methodology

An interventional, 12 weeks (core) & 12 weeks (first extension), multicenter, double-blind, double-dummy, active-controlled clinical study to treat patients with acute flares of gout and to prevent new gout flares. Patients were randomized to canakinumab 150 mg or triamcinolone acetonide 40 mg in a 1:1 ratio.

Patients who participated in the first extension study (CACZ885H2356E1) continued to be treated in the second extension (E2) study for any new gout flare on demand with one sc injection of canakinumab 150 mg.

Centres

Total of 57 centers in the core study: Australia (1), Belgium (1), Canada (5), Colombia (4), Estonia (4), Germany (3), Guatemala (2), Latvia (4), Lithuania (6), Mexico (3), Norway (1), Poland (2), Russia (11), Singapore (1), Sweden (1), Switzerland (1 [principal investigator, without patients]), Ukraine (7).

Total of 48 centers in first extension study: Australia (1), Belgium (1), Canada (3), Colombia (4), Estonia (4), Germany (3), Guatemala (2), Latvia (4), Lithuania (6), Poland (2), Russia (8), Singapore (1), Sweden (1), Switzerland (1 [principal investigator, without patients]), Ukraine (7).

Total of 33 centers in second extension study: Australia (1), Belgium (1), Canada (2), Estonia (4), Germany (3), Latvia (3), Lithuania (5), Poland (2), Russia (5), Singapore (1), Sweden (1), Switzerland (1 [principal investigator, without patients]), Ukraine (4).

Objectives

Primary objective(s)

Core study: two co-primary objectives:

- To investigate that canakinumab 150 mg subcutaneous (s.c.) was superior to triamcinolone acetonide 40 mg intramuscular (i.m.) with respect to patient's assessment of gout pain intensity in the most affected joint at Baseline at 72 hours post-dose (on a 0-100 mm Visual Analog Scale (VAS))
- To investigate that canakinumab 150 mg s.c. was superior to triamcinolone acetonide 40 mg i.m. with respect to the time to the first new gout flare

First extension study:

- To investigate the long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m.

Second extension study:

- To confirm the long-term safety and tolerability of canakinumab 150 mg sc over 18 months

Secondary objectives

Core study

- To evaluate time to complete resolution of pain in the most affected joint at Baseline (Likert scale)
- To evaluate time to 50% reduction of baseline pain intensity in the most affected joint
- To evaluate the proportion of patients taking rescue medication
- To evaluate the SF-36 physical function component score

First extension study

- To evaluate the time to the first new gout flare during 24 weeks
- To evaluate the frequency of new gout flares during 24 weeks

Second extension study

- To evaluate the long-term efficacy of canakinumab 150 mg sc with respect to the treatment of signs and symptoms of new gout flares, defined as:
  - Time to the first new gout flare
  - Frequency of new gout flares

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

Canakinumab 150 mg:

Patients received 1 s.c. injection of canakinumab 150 mg and 1 i.m. injection of placebo to triamcinolone acetonide on Day 1. Patients could receive a re-dose of study drug on demand upon the occurrence of new flares, but re-dosing could not occur until 14 days had elapsed after the previous dose. Patients completing the 12 weeks core study continued to be treated in another 12 weeks extension study for any new gout flare on demand with the same treatment as assigned in the core study.

In the second extension study, all patients were to receive canakinumab 150 mg sc, given on demand upon new flares.

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

Triamcinolone acetonide 40 mg:

Patients received 1 i.m. injection of triamcinolone acetonide 40 mg and 1 s.c. injection of placebo to canakinumab on Day 1. Patients could receive a re-dose of study drug on demand upon the occurrence of new flares, but re-dosing could not occur until 14 days had elapsed after the previous dose. Patients completing the 12 weeks core study continued to be treated in another 12 weeks extension study for any new gout flare on demand with the same treatment as assigned in the core study.

In the second extension study, all patients randomized to triamcinolone acetonide 40 mg were to switch treatment and were to receive canakinumab 150 mg sc, given on demand upon new flares.

Criteria for Evaluation

Efficacy:

Efficacy assessments consisted of pain intensity measurements using a 0-100 mm VAS and a 5-point Likert scale; rescue medication intake.

Safety:

Safety assessments consisted of collecting all adverse events (AEs) and serious adverse events (SAEs), with their severity and relationship to study drug; and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine; regular assessments of vital signs, physical condition, and body weight; ECG; and local tolerability at the s.c. and i.m. injection sites.

Health-related quality of life:

Medical Outcome Short Form (36) Health Survey (SF-36v2®, acute form)

Statistical Methods

Both co-primary objectives had to be met in the core study so there was no adjustment for multiplicity. The hypotheses were tested at a one-sided 2.5% level. Treatment difference in pain intensity in the most affected joint on a VAS at 72 hours post-dose was analyzed by an analysis of covariance with treatment group, baseline VAS score and BMI at baseline as covariates.

Treatment difference for time to first new gout flares was analyzed using a Cox proportional hazard regression model with treatment and BMI at baseline as explanatory variables.

A hypothesis of superiority of Canakinumab 150mg to triamcinolone acetonide 40 mg i.m. with respect to the time to the first new flare during 24 weeks in the extension study was tested at a one-sided 2.5% level.

All other secondary variables were analyzed using two-sided tests.

In order to control the type I error, the secondary variables were split into two sets in the core study.

The first set consisted of the following variables:

- Time to complete resolution of pain in the most affected joint (pain intensity on Likert = none)
- Time to 50 % reduction of baseline pain intensity in the most affected joint (VAS)
- Proportion of a patients taking rescue medication during the first week
- SF-36 physical function component score at Week 12

The Bonferroni-Holm method was used to adjust for multiplicity in the evaluation of these secondary efficacy variables.

All other variables in the core study were analyzed in the second set without adjustment for multiplicity.

The secondary variables were analyzed using Cox's proportional hazards regression, Kaplan-Meier analyses, logistic regression, negative binominal analysis, analysis of covariance, and proportional odds regression where appropriate.

Baseline response variable and BMI at baseline were included as covariates in the analyses.

Summaries were provided by treatment group for adverse events, laboratory values, vital signs and tolerability. Adverse events in patients who were and were not re-treated were summarized. Local injection site tolerability assessed on the injection site was summarized by injection type and treatment group.

First extension study

The data analysis in the first extension study was the follow-up analysis from the core study including all the data from both the core and extension studies.

No interim analysis was performed for the core or first extension studies.

Second extension study

The data analysis was a follow-up analysis from the core and the first extension studies including all data from the core, the first and the second extension studies. Data were summarized with respect to demographic and baseline characteristics (from the core study), efficacy observations and measurements, safety observations and measurements.

The Full Analysis Set (FAS) consisted of all patients as randomized in the core study who took at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.

The Modified Analysis Set (MAS) consisted of all FAS patients. Patients were analyzed according to treatment received. Patients who received both treatments were presented in both

treatment groups according to their exposure.

The Safety Set consisted of all patients who received study drug in the core study and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received. Patients who received both treatments were presented in both treatment groups according to their exposure.

Summaries were provided by treatment group for adverse events, laboratory values, vital signs and tolerability for the Safety Set according to the latest treatment received.

Adverse events were coded using the MedDRA dictionary that provided the primary system organ class and preferred term information. Adverse events were summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event based on the preferred term. Deaths, serious adverse events, and adverse events leading to discontinuation of study drug were summarized by primary system organ class and preferred term.

Summaries of adverse events were also produced by adjusting for the time of exposure.

Local injection site tolerability was assessed at the injection site.

All efficacy analyses were performed using the FAS or the MAS. All variables were analyzed using two-sided tests. No adjustment was made for multiplicity and each variable was analyzed using an alpha-level of 0.05. Time to first new gout flare was tested for the superiority of canakinumab 150 mg sc to triamcinolone acetonide 40 mg im using the FAS at a one-sided 2.5% level. The efficacy variables were summarized for baseline; 1st, 2nd and the last post-baseline flare treated with canakinumab 150 mg sc.

Two interim analyses were performed to support health authority submissions. The first interim analysis had its cut-off on 15-Mar-2011 and was used to provide data in the Food and Drug Administration (FDA) 120 day safety update submitted in May-2011.

The second interim analysis had its cut-off date on 15-Jul-2011 and was used for preparing the Clinical Addendum submitted to the FDA in Aug-2011 and answering the RSI (Request for supplementary information) submitted to the European Medicines Agency in Oct-2011.

Study Population: Inclusion/Exclusion Criteria and Demographics

Ages Eligible for Study: 18 Years to 85 Years
Genders Eligible for Study: Both

Core study:

Inclusion criteria:

- Signed written informed consent before any study procedure was performed.
- Meeting the American College of Rheumatology (ACR) 1977 preliminary criteria for the classification of acute arthritis of primary gout
- Onset of current acute gout flare within 5 days prior to study entry
- Baseline pain intensity ≥ 50 mm on the 0-100 mm visual analog scale (VAS)
- History of ≥ 3 gout flares within the 12 months prior to study entry
- Contraindication, intolerance, or lack of efficacy for non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine

Exclusion criteria:

- Rheumatoid arthritis, evidence/suspicion of infectious/septic arthritis, or other acute inflammatory arthritis
- Presence of severe renal function impairment
- Use of specified pain relief medications or biologics (corticosteroids, narcotics, paracetamol/ acetaminophen, ibuprofen, colchicine, IL-blocker, and tumor necrosis factor inhibitor) within specified periods prior to study entry
- Live vaccinations within 3 months prior to randomization
- Requirement for administration of antibiotics against latent tuberculosis (TB)
- Refractory heart failure (Stage D)
- Unstable cardiac arrhythmias or unstable symptomatic coronary ischemia
- Any active or recurrent bacterial, fungal, or viral infection
- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception, confirmed by a positive pregnancy test (serum or urine), and until the termination of gestation.
- Female patients being physiologically capable of becoming pregnant UNLESS they were:
  - Female patients whose career, lifestyle, or sexual orientation precluded intercourse with a male partner
  - Female patients whose partners have been sterilized by vasectomy or other means
  - Using an acceptable method of contraception with a failure rate (Pearl Index (PI)) < 1, reliable contraception should be maintained throughout the study and for 2 months after last study drug administration.

First extension study:

Inclusion:

- Signed written informed consent before any study procedure was performed.
- Completion of the Core study. A patient was defined as completing the core study if they completed the study up to and including visit 7.

Exclusion:

- Continuation in this extension study was considered inappropriate by the treating physician.
- Pregnant or nursing (lactating) women, (same definition as in core study; see above).
- Female patients being physiologically capable of becoming pregnant (same definition as in core study; see above)

Second extension study:

Inclusion:

- Signed written informed consent before any study procedure was performed.
- Completion of the first extension study. A patient was defined as completing the first extension study if they completed the study up to and including visit 10.

Exclusion:

- Continuation in this extension study was considered inappropriate by the treating physician.
- Pregnant or nursing (lactating) women, (same definition as in core study; see above).
- Female patients being physiologically capable of becoming pregnant (same definition as in core study; see above).

No additional exclusions could be applied by the investigator, in order to ensure that the study population was representative of all eligible patients.

Number of Subjects

Core Study (0-12 Weeks)

	ACZ885 150 mg s.c. N=115 n (%)	Triam 40 mg i.m. N=115 n (%)
Planned N	110	110
Randomised n	115 (100)	115 (100)
Full Analysis Set (FAS), Safety Set	113 (98.2)	115 (100)
Completed n (%)	109 (94.8)	105 (91.3)
Not completed n (%)	6 (5.2)	10 (8.7)
Withdrawn due to lack of efficacy n (%)	0 (0.0)	4 (3.5)
Patient withdrew consent n (%)	1 (0.9)	3 (2.6)
Withdrawn due to administrative reason n (%)	2 (1.7)	1 (0.9)
Lost to Follow-up (%)	3 (2.6)	1 (1.9)
Death (%)	0 (0.0)	1 (1.9)

First Extension Study (12-24 Weeks)

	ACZ885 150 mg s.c. N=90 n (%)	Triam 40 mg i.m. N=85 n (%)
Completed the Core n	109	105
Entered the extension 1 phase n (%)	90 (100)	85 (100)
Completed the extension 1 phase n (%)	87 (96.7)	80 (88.9)
Not completed (core and extension) n (%)	3 (3.3)	5 (5.5)
Withdrawn due to lack of efficacy n (%)	0 (0.0)	1 (1.1)
Patient withdrew consent n (%)	0 (0.0)	1 (1.1)
Lost to Follow-up (%)	2 (2.2)	3 (3.3)
Protocol Deviation (%)	1 (1.1)	0 (0.0)

Number of Subjects: Core + Both Extension Studies

	ACZ885 150mg sc (N=115)		Triam** 40mg im (N=115)		
	All ACZ N=115 n (%)	Re-treated with ACZ N=69 n (%)	All Triam N=115 n (%)	Treated with ACZ N=39 n (%)	Total N=230 n (%)
Completed core study	109 (94.8)	69 (100.0)	105 (91.3)	39 (100.0)	214 (93.0)
Discontinued core study	6 (5.2)	0 (0.0)	10 (8.7)	0 (0.0)	16 (7.0)
Entered extension 1 study	90 (78.3)	65 (94.2)	85 (73.9)	39 (100.0)	175 (76.1)
Completed extension 1 study	87 (75.7)	65 (94.2)	80 (69.6)	39 (100.0)	167 (72.6)
Discontinued extension 1 study	3 (2.6)	0 (0.0)	5 (4.3)	0 (0.0)	8 (3.5)
Entered extension 2 study	69 (60.0)	57 (82.6)	66 (57.4)	39 (100.0)	135 (58.7)
Completed extension 2 study	68 (59.1)	56 (81.2)	63 (54.8)	38 (97.4)	131 (57.0)
Discontinued extension 2 study	1 (0.9)	1 (1.4)	3 (2.6)	1 (2.6)	4 (1.7)
Discontinued core, extension 1 or extension 2 study	10 (8.7)	1 (1.4)	18 (15.7)	1 (2.6)	28 (12.2)
Reason for discontinuation					
Adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal laboratory value(s)	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)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	5 (4.3)	0 (0.0)	5 (2.2)
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	1 (0.9)	0 (0.0)	5 (4.3)	0 (0.0)	6 (2.6)
Lost to follow-up	5 (4.3)	0 (0.0)	5 (4.3)	1 (2.6)	10 (4.3)
Administrative problems	2 (1.7)	0 (0.0)	1 (0.9)	0 (0.0)	3 (1.3)
Death	1 (0.9)	1* (1.4)	2 (1.7)	0 (0.0)	3 (1.3)
Protocol deviation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

*This patient is also represented in the “All ACZ” column.
**Triam=triamcinolone acetonide
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.

Demographic and Background Characteristics (core and first extension study)

	ACZ885 150 mg s.c. N=113 n (%)	Triam 40 mg i.m. N=115 n (%)
Sex – n (%)		
Male	101 (89.4)	108 (93.9)
Female	12 (10.6)	7 (6.1)
Age (years)		
Mean	54.0	54.6
SD	11.18	10.71
Median	54.0	55.0
Min	31	28
Max	82	85
Age groups – n (%)		
< 65 years	92 (81.4)	92 (80.0)
≥ 65 – 74 years	16 (14.2)	21 (18.3)
≥ 75 years	5 (4.4)	2 (1.7)
Race		
Caucasian	93 (82.3	96 (83.5)
Black	0 (0.0	0 (0.0)
Asian	3 (2.7)	3 (2.6)
Native American	1 (0.9)	1 (0.9)
Pacific Islander	0 (0.0)	0 (0.0)
Other	16 (14.2)	15 (13.0)
BMI (kg/m^2		
Mean	31.84	31.57
SD	4.710	4.745
Median	31.17	31.15
Min	22.5	21.5
Max	44.2	44.5

Disease characteristics by treatment group (core and first extension study)

	ACZ885 150 mg s.c. N=113 n (%)	Triam 40 mg i.m. N=115 n (%)
No. of flares in previous year		
n	113	115
Mean	6.5	7.0
SD	5.52	5.10
Median	4.0	5.0
Min	3	3
Max	36	30
No. of joints affected by acute attack of gout within the last 5 days – n (%)		
1	57 (50.4)	59 (51.3)
2	23 (20.4)	26 (22.6)
3	7 (6.2)	13 (11.3)

4	6 (5.3)	5 (4.3)
> 4	20 (17.7)	12 (10.4)
Contraindicated to		
NSAIDs	61 (54.0)	50 (43.5)
Colchicine	10 (8.8)	12 (10.4)
Both	7 (6.2)	9 (7.8)
Intolerant to		
NSAIDs	44 (38.9)	40 (34.8)
Colchicine	16 (14.2)	20 (17.4)
Both	9 (8.0)	10 (8.7)
Lack of efficacy for		
NSAIDs	75 (66.4)	86 (74.8)
Colchicine	14 (12.4)	21 (18.3)
Both	10 (8.8)	16 (13.9)
Contraindicated, intolerant, or lack of efficacy for		
NSAIDs	107 (94.7)	113 (98.3)
Colchicine	27 (23.9)	39 (33.9)
Both	22 (19.5)	38 (33.0)
Pain (0 – 100 mm VAS)		
n	112	111
Mean	73.3	74.8
SD	11.37	12.65
Median	73.5	75.0
Min	47	46
Max	99	100
Pain (5-point Likert scale) – n (%)		
Mild	1 (0.9)	2 (1.7)
Moderate	25 (22.1)	27 (23.5)
Severe	75 (66.4)	74 (64.3)
Extreme	11 (9.7)	11 (9.6)
Tophi present – n (%)		
Yes	44 (38.9)	45 (39.1)
No	69 (61.1)	70 (60.9)
Current user of urate lowering therapy (ULT) – n (%)		
Yes	57 (50.4)	63 (54.8)
No	56 (49.6)	52 (45.2)

Demographic and Background Characteristics (second extension study)

	Randomized to ACZ885 150mg sc (N=113)		Randomized to Triam 40mg im (N=115)	
Demographic variable	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%)
Female	12 (10.6%)	6 (8.7%)	7 (6.1%)	2 (5.1%)
Age (years)				
n	113	69	115	39
Mean (SD)	54.0 (11.18)	52.4 (10.19)	54.6 (10.71)	55.3 (12.80)
Median	54.0	52.0	55.0	54.0
Min, Max	31, 82	33, 78	28, 85	28, 85
Age groups				
< 65 years	92 (81.4%)	60 (87.0%)	92 (80.0%)	28 (71.8%)
≥ 65-74 years	16 (14.2%)	8 (11.6%)	21 (18.3%)	9 (23.1%)
≥ 75 years	5 (4.4%)	1 (1.4%)	2 (1.7%)	2 (5.1%)
Race				
Caucasian	93 (82.3%)	59 (85.5%)	96 (83.5%)	38 (97.4%)
Black	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%)
Native American	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Pacific islander	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]
BMI (kg/m2)**				
n	113	69	115	39
Mean (SD)	31.84 (4.710)	31.38 (4.673)	31.57 (4.745)	32.24 (4.682)
Median	31.17	31.17	31.15	32.25
Min, Max	22.5, 44.2	22.8, 44.2	21.5, 44.5	22.2, 41.2

Disease characteristics by treatment group (second extension study)

	Randomized to ACZ885 150mg sc (N=113)		Randomized to Triam 40mg im (N=115)	
Variable	All ACZ N=113	Re-treated with ACZ N=69	All Triam N=115	Switched to ACZ N=39
No. of joints affected by acute attack of gout within the last 5 days				
1	57 (50.4%)	37 (53.6%)	59 (51.3%)	20 (51.3%)
2	23 (20.4%)	9 (13.0%)	26 (22.6%)	9 (23.1%)
3	7 (6.2%)	4 (5.8%)	13 (11.3%)	4 (10.3%)
4	6 (5.3%)	3 (4.3%)	5 (4.3%)	3 (7.7%)
> 4	20 (17.7%)	16 (23.2%)	12 (10.4%)	3 (7.7%)
Contraindicated to				
NSAIDs	61 (54.0%)	35 (50.7%)	50 (43.5%)	17 (43.6%)
Colchicine	10 (8.8%)	4 (5.8%)	12 (10.4%)	1 (2.6%)
Both	7 (6.2%)	1 (1.4%)	9 (7.8%)	1 (2.6%)
Intolerant to				

NSAIDs	44 (38.9%)	28 (40.6%)	40 (34.8%)	10 (25.6%)
Colchicine	16 (14.2%)	8 (11.6%)	20 (17.4%)	7 (17.9%)
Both	9 (8.0%)	4 (5.8%)	10 (8.7%)	1 (2.6%)
Lack of efficacy for				
NSAIDs	75 (66.4%)	45 (65.2%)	86 (74.8%)	29 (74.4%)
Colchicine	14 (12.4%)	7 (10.1%)	21 (18.3%)	1 (2.6%)
Both	10 (8.8%)	5 (7.2%)	16 (13.9%)	1 (2.6%)
Contraindicated, intolerant or lack of efficacy for				
NSAIDs	107 (94.7%)	66 (95.7%)	113 (98.3%)	38 (97.4%)
Colchicine	27 (23.9%)	14 (20.3%)	39 (33.9%)	8 (20.5%)
Both	22 (19.5%)	11 (15.9%)	38 (33.0%)	7 (17.9%)
Pain (5-point Likert Scale)				
Mild	1 (0.9%)	0 (0.0%)	2 (1.7%)	2 (5.1%)
Moderate	25 (22.1%)	14 (20.3%)	27 (23.5%)	11 (28.2%)
Severe	75 (66.4%)	46 (66.7%)	74 (64.3%)	23 (59.0%)
Extreme	11 (9.7%)	8 (11.6%)	11 (9.6%)	3 (7.7%)
Joint tenderness				
No pain	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Pain	20 (17.7%)	12 (17.4%)	26 (22.6%)	7 (17.9%)
Pain and winces	51 (45.1%)	30 (43.5%)	50 (43.5%)	21 (53.8%)
Pain, winces and with-draws	42 (37.2%)	27 (39.1%)	38 (33.0%)	11 (28.2%)
Joint swelling				
No swelling	0 (0.0%)	0 (0.0%)	3 (2.6%)	1 (2.6%)
Palpable	10 (8.8%)	9 (13.0%)	7 (6.1%)	1 (2.6%)
Visible	66 (58.4%)	33 (47.8%)	72 (62.6%)	25 (64.1%)
Bulging beyond the joint margins	37 (32.7%)	27 (39.1%)	33 (28.7%)	12 (30.8%)
Erythma				
Absent	13 (11.5%)	7 (10.1%)	17 (14.8%)	3 (7.7%)
Present	99 (87.6%)	62 (89.9%)	96 (83.5%)	34 (87.2%)
Not assessable	1 (0.9%)	0 (0.0%)	2 (1.7%)	2 (5.1%)
C-reactive protein (mg/L)				
n	110	67	113	39
Mean (SD)	33.5 (52.77)	36.7 (59.84)	25.5 (42.15)	27.8 (32.73)
Median	13.2	13.8	9.4	11.8
Min, Max	0, 346	1, 346	1, 278	1, 136
Serum amyloid A protein (mg/L)				
n	113	69	113	39
Mean (SD)	133.2 (321.72)	149.6 (379.17)	76.9 (180.39)	90.5 (155.94)
Median	18.0	18.3	9.9	12.0
Min, Max	1, 2500	1, 2500	0, 1080	2, 595
Current user of ULT				
Yes	57 (50.4%)	31 (44.9%)	63 (54.8%)	26 (66.7%)
No	56 (49.6%)	38 (55.1%)	52 (45.2%)	13 (33.3%)
Known presence of tophi				
Yes	44 (38.9%)	29 (42.0%)	45 (39.1%)	15 (38.5%)

No	69 (61.1%)	40 (58.0%)	70 (60.9%)	24 (61.5%)

Primary Objective Result(s)

Core Study

Pain intensity measured by 0-100 mm VAS at 72 hours post-dose

Treatment	N	LS Mean	Standard Error	Estimated Difference to Triam 40 mg i.m.	95%CI	One-sided p-value
ACZ885 150 mg s.c.	112	28.1	2.42	-11.4	(-18.2, -4.6)	0.0005 *
Triam 40 mg i.m.	111	39.5	2.44	---	---	---

ANCOVA with treatment group, baseline VAS score for that flare and BMI at baseline as covariates.
* denotes a p-value ≤0.025.

Time to first new gout flare

		Kaplan-Meier estimate		Cox's proportional hazard regression model		
Treatment	N	End of study (%)	95% CI	Hazard ratio to Triam 40 mg .m.	95% CI	One-sided p-value
ACZ885 150 mg s.c.	113	18.9	(12.7 - 27.5)	0.45	(0.26 - 0.76)	0.0014 *
Triam 40 mg i.m.	115	36.5	(28.3 - 46.3)	---	---	---

Cox's proportional hazard regression model with treatment group and BMI at baseline as covariates.
* denotes a p-value ≤0.025.

First Extension Study

As the primary objective of the first extension study was to confirm the long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m., there is no primary efficacy variable. All efficacy variables are part of the secondary objectives of the study.

Second Extension Study

As the primary objective of the second extension study was to confirm the long-term safety and tolerability of canakinumab 150 mg sc over 18 months, there is no primary efficacy variable. All efficacy variables are part of the secondary objectives of the study.

Secondary Objective Results

Core Study (0-12 Weeks)

First set secondary efficacy variables

Endpoint	ACZ885 150 mg s.c. vs. Triam 40 mg i.m.	95% CI	Two-sided p-value
Proportion of patients taking rescue medication (odds ratio)	0.42	(0.24, 0.73)	0.0022 *
Time to 50% reduction of baseline pain intensity (hazard ratio)	1.47	(1.10, 1.97)	0.0103 *
Time to complete resolution of pain (hazard ratio)	1.09	(0.69, 1.71)	0.7227
SF-36 (physical component) at end of study (estimated difference)	0.27	(-7.31,7.85)	0.9431

(1) p-values are sorted in ascending order
* denotes a significant p-value

Bonferroni-Holm adjustment is used to adjust for multiplicity in the evaluation of these first set secondary endpoints.

Core & First Extension Study (0-24 Weeks)

Time to first new flare

		Kaplan-Meier estimate		Cox's proportional hazard regression model		
Treatment	N	Median (days)	95% CI	Hazard ratio to Triam 40 mg i.m.	95% CI	One-sided p-value
ACZ885 150 mg s.c.	113	NotEst	(NotEst - NotEst)	0.48	(0.32 - 0.73)	0.0003 *
Triam 40 mg i.m.	115	119.0	(94.0 - NotEst)	---	---	---

NotEst=nonestimable

Cox's proportional hazard regression model with treatment group and BMI at baseline as covariates.
* denotes a p-value ≤0.025.

Percentage of patients with at least one new gout flare

Treatment	N	Incidence rate (1) n (%)	Estimated odds ratio to Triam 40 mg	95%CI of odds ratio	Two-sided p-value
ACZ885 150 mg s.c.	113	36 (31.9)	0.44	(0.26, 0.76)	0.0030 *
Triam 40 mg i.m.	115	59 (51.3)	---	---	---

Logistic regression with treatment group and BMI at baseline as covariates.

An odds ratio >1 indicates that a gout flare is more likely to occur with ACZ885 150 mg s.c. in comparison to the Triam 40 mg i.m. group.

(1) Incidence rate: number of patients who had at least one new gout flare after randomization.

* denotes a p-value ≤0.05.

Second extension study:

Time to first new flare: Survival analysis by treatment

Kaplan-Meier estimate				Cox's proportional hazard regression model			
Randomized treatment	**N**	**Median (days)**	**95% Confidence Interval**	**N**	**Hazard ratio to Triam 40mg**	**95% Confidence Interval**	**One-sided p-value**
ACZ885 150mg sc	113	222.0	(190.0 - 274.0)	113	0.84	(0.60 - 1.17)	0.1483
Triam 40mg im	115	119.0	(94.0 - 224.0)	115			

Cox's proportional hazard regression model with treatment group and BMI at baseline as covariates.
* denotes a p-value ≤ 0.025

Flare rate per year: ratio estimate of treatment effect from negative binomial model

Rate (flares/year)				Rate ratio			
Randomized treatment	**N**	**Mean flare rate per year**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Two-sided p-value**
ACZ885 150mg sc	113	1.16	1.21	(0.97, 1.51)	0.56	(0.41, 0.77)	0.0004 *
Triam 40mg im	115	2.81	2.16	(1.72, 2.71)			

Rate ratio ACZ885 150mg sc/Triam 40mg im is estimated from negative binomial model with treatment group and BMI at baseline as covariates and log (time on study) as an offset.
* denotes a p-value < 0.05.

Safety Results

Adverse Events by System Organ Class

Core & First Extension Studies (0-24 Weeks)

	ACZ885 150 mg s.c. N=113 n (%)	Triam 40 mg i.m. N=115 n (%)
Total no. of patients with AE(s)	71 (62.8)	56 (48.7)
Infections and infestations	25 (22.1)	18 (15.7)
Musculoskeletal and connective tissue disorders	19 (16.8)	11 (9.6)
Nervous system disorders	17 (15.0)	6 (5.2)
Investigations	16 (14.2)	9 (7.8)
Metabolism and nutrition disorders	16 (14.2)	11 (9.6)
Vascular disorders	12 (10.6)	10 (8.7)
Gastrointestinal disorders	9 (8.0)	8 (7.0)
Cardiac disorders	8 (7.1)	6 (5.2)
Skin and subcutaneous tissue disorders	7 (6.2)	3 (2.6)
Blood and lymphatic system disorders	6 (5.3)	3 (2.6)
Renal and urinary disorders	6 (5.3)	3 (2.6)
General disorders and administration site conditions	5 (4.4)	4 (3.5)
Eye disorders	4 (3.5)	0
Psychiatric disorders	4 (3.5)	2 (1.7)
Injury, poisoning and procedural complications	3 (2.7)	6 (5.2)
Ear and labyrinth disorders	2 (1.8)	1 (0.9)
Hepatobiliary disorders	2 (1.8)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	2 (1.8)	2 (1.7)
Social circumstances	0	1 (0.9)

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

Core & First Extension Studies (0-24 Weeks)

	ACZ885 150 mg s.c. N=113 n (%)	Triam 40 mg i.m. N=115 n (%)
Total no. of patients with AE(s)	71 (62.8)	56 (48.7)
Headache	7 (6.2)	2 (1.7)
Hypertension	7 (6.2)	8 (7.0)
Gamma-glutamyltransferase increased	6 (5.3)	2 (1.7)
Arthralgia	5 (4.4)	1 (0.9)
Back pain	5 (4.4)	0
Hypertriglyceridemia	5 (4.4)	0
Nasopharyngitis	5 (4.4)	1 (0.9)
Osteoarthritis	5 (4.4)	1 (0.9)
Gout	0	5 (4.3)

Second Extension Study

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

	ACZ885 150mg sc (N=113)			Triam 40mg im (N=115)		
		Re-treated with ACZ (N=69)			Treated with ACZ (N=39)	
Preferred term	All ACZ N=113 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)	All Triam N=115 n (IR/ 100 pyr)	Before (1) n (IR/ 100 pyr)	After (1) n (IR/ 100 pyr)
All preferred terms	336 (302.4)	136 (400.1)	112 (224.3)	186 (238.3)	56 (205.7)	37 (137.7)
Hypertension	17 (15.3)	6 (17.7)	8 (16.0)	12 (15.4)	5 (18.4)	4 (14.9)
Headache	14 (12.6)	3 (8.8)	2 (4.0)	5 (6.4)	0	1 (3.7)
Arthralgia	12 (10.8)	3 (8.8)	8 (16.0)	3 (3.8)	3 (11.0)	1 (3.7)
Gamma-glutamyltransferase increased	9 (8.1)	5 (14.7)	1 (2.0)	5 (6.4)	1 (3.7)	0
Nasopharyngitis	8 (7.2)	4 (11.8)	2 (4.0)	3 (3.8)	2 (7.3)	2 (7.4)
Bronchitis	3 (2.7)	1 (2.9)	1 (2.0)	4 (5.1)	3 (11.0)	3 (11.2)
Osteoarthritis	7 (6.3)	1 (2.9)	2 (4.0)	2 (2.6)	0	0
Upper respiratory tract infection	3 (2.7)	2 (5.9)	1 (2.0)	3 (3.8)	2 (7.3)	3 (11.2)
Back pain	7 (6.3)	4 (11.8)	2 (4.0)	0	0	1 (3.7)
Influenza	5 (4.5)	1 (2.9)	4 (8.0)	1 (1.3)	0	1 (3.7)
Hypertriglyceridemia	5 (4.5)	4 (11.8)	0	0	0	1 (3.7)
Hyperlipidemia	0	0	0	1 (1.3)	0	2 (7.4)

Preferred terms are sorted by descending frequency of the total number observed for all ACZ 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 patients' times at risk, i.e. duration of exposure until the date of last study day.
(1) First treatment/re-treatment with ACZ.

Serious Adverse Events and Deaths

Core & First Extension Studies (0-24 Weeks)

	ACZ885 150 mg s.c. N=113 n (%)	Triam 40 mg i.m. N=115 n (%)
Death(s)	0	1 (0.9)
SAE(s)	11 (9.7)	6 (5.2)
Discontinuation due to AE(s)	0	0

Note: One patient in the triamcinolone acetonide group discontinued from the study due to an SAE of pulmonary embolism and subsequently died.

Deaths, other serious adverse events or related discontinuations (Core & both extension studies)

	Randomized to ACZ885 150mg sc (N=113)			Randomized to Triam 40mg im (N=115)		
		Re-treated with ACZ (N=69)			Switched to ACZ (N=39)	
	All ACZ N=113 n (%)	Before (1) n (%)	After (1) n (%)	All Triam N=115 n (%)	Before (1) n (%)	After (1) n (%)
Deaths	1 (0.9)	0 (0.0)	1 (1.4)	2 (1.7)	0 (0.0)	0 (0.0)
SAEs	19 (16.8)	6 (8.7)	8 (11.6)	11 (9.6)	2 (5.1)	0 (0.0)
Discontinued due to AE(s)	1 (0.9)	0 (0.0)	1 (1.4)	2 (1.7)	0 (0.0)	0 (0.0)
Discontinued due to SAE(s), including fatal SAE(s)	1 (0.9)	0 (0.0)	1 (1.4)	2 (1.7)	0 (0.0)	0 (0.0)
Discontinued due to non-serious AE(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Deaths: One patient in the triamcinolone acetonide group experienced an SAE of pulmonary embolism on Day 10 of the core study, and he died on the same day due to sudden cardiovascular death.

No deaths occurred during the first extension study. There were two deaths during the second extension study: One patient in the re-treated canakinumab group (only re-treatment on Day 214), died of severe pneumonia on Day 323. One patient who was originally randomized to the triamcinolone acetonide group and not re-treated died of pneumococcal sepsis.

SAEs: Core study SAEs in the canakinumab group: 1 angina pectoris, 1 arrhythmia, 1 myocardial ischemia, 1 glaucoma, 1 retinal artery occlusion, 1 spinal cord ischemia, 1 infection (abscess jaw), 1 gastritis with chronic renal failure, 1 prostatic specific antigen increased, 1 hyperglycemia and 1 device dislocation (hip endoprosthesis).

Core study SAEs in the triamcinolone acetonide group: 1 ischemic stroke, 1 vertebrobasilar insufficiency, 1 pulmonary embolism, 1 meniscus lesion and 1 gout.

First extension study: Two patients experienced SAEs during the first extension study: 1 pneumonia in the canakinumab group and 1gout in the triamcinolone acetonide group.

SAEs during second extension study: 11 patients on canakinumab treatment reported 15 SAEs, including 3 who had SAEs in the core or first extension study (pneumonia, renal impairment, hyperkalemia, cerebrovascular accident (2 patients), device dislocation, deep vein thrombosis, acute myocardial infarction, fibula fracture, intestinal diverticulum, colon cancer, transient ischemic attack, renal colic, nephrolithiasis and unstable angina. Six patients on triamcinolone acetonide reported 11 SAEs, including 1 who had an SAE during the core study (basal cell carcinoma, periproctitis, radiculopathy, renal colic, device related infection, septic shock, staphylococcal infection, endocarditis, cardiac failure, pneumonia and unstable angina.

Other Relevant Findings

NA

Date of Clinical Trial Report CSR published CACZ885H2356 (core study), 11 Nov 2010 CACZ885H2356E1 (first extension included in core report), 13 Dec 2010 CACZ885H2356E2 (second extension included in core report), 25 Sep 2012
Date Inclusion on Novartis Clinical Trial Results Database CACZ885H2356, 14 October 2011 CACZ885H2356 with first extension, 14 October 2011 CACZ885H2356 with first and second extensions, 25 September 2012
Date of Latest Update 21 September 2012