Sponsor

Novartis

Generic Drug Name

Canakinumab / ACZ885

Trial Indication(s)

Gouty arthritis

Protocol Number

CACZ885H2357E1

Protocol Title

A randomized, controlled extension study of CACZ885H2357 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

Study Start/End Dates

30-Jun-2010 to 25-Nov-2010

Reason for Termination

Not applicable.

Study Design/Methodology

Patients completing the core study CACZ885H2357 were invited to enter this 12-week, multicenter, double-blind, double-dummy, active-controlled extension study to provide additional data and to continue to investigate “on demand” use of

canakinumab 150 mg s.c. or triamcinolone acetonide 40 mg i.m upon flare. Patients continued to be treated in this extension study for any new gout flare on demand with the same treatment as assigned in the core study.

Centers

65 centers in the extension study: Canada (2), The Netherlands (1), Russia (4), Taiwan (4), and United States (53)

Objectives:

Primary objective(s)

The primary objective was to confirm the long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m.

Secondary objective(s)

To evaluate the time to the first new gout flare
- To evaluate the frequency of new gout flares
- To evaluate the severity of new gout flares
- To evaluate the efficacy with respect to the treatment of signs and symptoms of each new gout flare, defined as:
    - Patient's assessment of gout pain intensity in the most affected joint (on a 0-100 mm VAS) over time
    - Patient's assessment of gout pain intensity in the most affected joint (Likert scale) over time
    - Patient's global assessment of response to treatment (Likert scale) over time
    - Physician's assessment of tenderness, swelling and erythema over time
    - Physician's assessment of range of motion of the most affected joint (Likert scale) over time
    - Physician's global assessment of response to treatment (Likert scale) over time
    - Rescue medication use during new gout flares with respect to:
        - Time to first rescue medication intake
        - Proportion of patients taking rescue medication
        - Amount of rescue medication taken

• To evaluate the efficacy with regards to inflammatory markers (high sensitivity C-reactive protein [hsCRP] and serum amyloid A [SAA] protein)
• To evaluate the immunogenicity
• To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD)

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

Patients received either one s.c. injection of canakinumab 150 mg and one i.m. injection of (triamcinolone acetonide-matching) placebo or one i.m. injection of triamcinolone acetonide 40 mg and one s.c. injection of (canakinumab matching) placebo on Day 1 of the core study. Patients could receive a re-dose on demand upon the occurrence of new flares in both the core and extension studies.

Statistical Methods

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

The primary objective of the analysis was to confirm the long-term safety and tolerability of canakinumab 150 mg s.c. compared to triamcinolone acetonide 40 mg i.m. in patients who were randomized in the core study.

Summaries were provided by treatment group for adverse events, laboratory values, vital signs and tolerability for the safety set using data collected during the core and extension phases of the study. 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.

Time to first new gout flare after entry into the core study was tested for the superiority of canakinumab 150 mg to triamcinolone acetonide 40 mg at a one-sided 2.5% level using a Cox proportional hazard regression model with treatment and BMI at baseline as explanatory variables.

All other efficacy variables for the last new flare were analyzed using two-sided tests. No adjustments were made for multiplicity and each variable was analyzed using an alpha-level of 0.05.

All efficacy analyses were performed using the full analysis set.

The secondary variables for the baseline, 1st, 2nd, and the last post-baseline flares were summarized up to 7 days by time point and were analyzed at the last post-baseline flare using Cox's proportional hazards regression, Kaplan-Meier analyses, logistic regression, analysis of covariance, and proportional odds regression where appropriate. Summaries were provided for some secondary variables in patients who were re-treated.

No interim analysis was performed for this study.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- 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, or intolerance, or lack of efficacy for non-steroidal anti-inflammatory drugs (NSAID) 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

Extension Study 1:

Inclusion:

- 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.

Extension Study 2:

Inclusion Criteria:
Completion of the first extension study CACZ885H2357E1. A patient was defined as completing the first extension study if they completed the study up to and including Visit 10).
Exclusion Criteria:
-Continuation in this second extension study was considered inappropriate by the treating physician.

Participant Flow Table

Period 1: Core Study (0- 12 Weeks)

	Canakinumab 150 mg	Triamcinolone Acetonide 40 mg
STARTED	**112**	**114**
COMPLETED	**99**	**103**
NOT COMPLETED	**13**	**11**
Abnormal laboratory value(s)	**1**	**1**
Patient withdrew consent	**6**	**4**
Lost to Follow-up	**5**	**3**
Administrative problems	**0**	**1**
Death	**1**	**0**
Protocol deviation	**0**	**2**

Period 2: Extension Study 1 (12 -24 Weeks)

	Canakinumab 150 mg	Triamcinolone Acetonide 40 mg
STARTED	**84**	**76**
COMPLETED	**78**	**72**

NOT COMPLETED	**6**	**4**
Adverse Event	**1**	**0**
Unsatisfactory Therapeutic Effect	**0**	**1**
Withdrawal by Subject	**4**	**3**
Lost to Follow-up	**1**	**0**

Period 3: Extension Study 2 (25-72 Weeks)

	Canakinumab 150 mg	**Triamcinolone Acetonide 40 mg**
STARTED	**72**	**65**
Re-treated With or Switch to Canakinumab	**62 [1]**	**41 [2]**
COMPLETED	**64**	**54**
NOT COMPLETED	**8**	**11**
Adverse Event	**1**	**2**
Withdrawal by Subject	**3**	**4**

[1] Includes patients re-treated with canakinumab at any time during the 72 weeks

[2] Includes patients switched to canakinumab from Week 25 - Week 72

Baseline Characteristics

Demographic and background characteristics by treatment group (Safety set)

	ACZ885 150 mg s.c. N=112	Triam 40 mg i.m. N=114	Total N=226
Sex – n (%)			
Male	100 (89.3)	105 (92.1)	205 (90.7)
Female	12 (10.7)	9 (7.9)	21 (9.3)
Age (years)			
n	112	114	226
Mean	50.6	52.6	51.6
SD	12.10	12.28	12.21
Median	51.0	53.0	52.0
Min	20	24	20
Max	78	79	79
Age groups – n (%)			
< 65 years	96 (85.7)	93 (81.6)	189 (83.6)
≥ 65-74 years	14 (12.5)	17 (14.9)	31 (13.7)
≥ 75 years	2 (1.8)	4 (3.5)	6 (2.7)
Race – n (%)			
Caucasian	74 (66.1)	80 (70.2)	154 (68.1)
Black	26 (23.2)	24 (21.1)	50 (22.1)
Asian	10 (8.9)	9 (7.9)	19 (8.4)
Native American	0	0	0
Pacific islander	0	0	0
Other	2 (1.8)	1 (0.9)	3 (1.3)

Summary of Efficacy

Primary Outcome Result(s)

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

		Kaplan-Meier estimate		Cox's proportional hazard regression model		
Treatment	N	Flare probability over 24 weeks (95% CI)	Median time to new flare – days (95% CI)	Hazard ratio to Triam 40 mg i.m.	95% CI	One-sided p-value
ACZ885 150 mg s.c.	112	29.1 (20.99, 39.44)	Not Est (Not Est, Not Est)	0.40	(0.25, 0.64)	<0.0001 *
Triam 40 mg i.m.	114	54.3 (44.12, 65.20)	146.0 (94.0, Not Est)			

Not Est=nonestimable
Cox's proportional hazard regression model with treatment group and BMI at baseline as covariates.
* denotes a p-value ≤0.025

Secondary Outcome Result(s)

Number of patients with new flares: Estimated odds ratio by treatment group (Full Analysis Set)

Treatment	N	Incidence rate (1) n (%)	Estimated odds ratio to Triam 40 mg i.m.	95%CI of odds ratio	Two-sided p-value
ACZ885 150 mg s.c.	112	28 (25.0)	0.39	(0.22, 0.68)	0.0010 *
Triam 40 mg i.m.	114	53 (46.5)			

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

Number of new gout flares per patient: Rate ratio estimate of treatment effect from negative binomial model (Full Analysis Set)

Treatment	N	Mean number of flares	Estimated rate ratio	95% CI	Two-sided p-value
ACZ885 150 mg s.c.	112	0.35	0.42	(0.27, 0.64)	0.0001*
Triam 40 mg i.m.	114	0.80			

Rate ratio 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

New flare compared to baseline flare: Mean (SD) VAS (0-100 mm) in patients who were re-treated (Full Analysis Set)

	ACZ885 150 mg s.c. N=25		Triam 40 mg i.m. N=46	
Time point	Baseline flare	New flare	Baseline flare	New flare
Baseline	72.6 (12.5)	67.4 (19.6)	75.8 (12.7)	73.2 (21.0)
6 hours post-dose	62.5 (20.7)	54.8 (25.5)	58.6 (24.4)	60.0 (24.0)
12 hours post-dose	57.0 (20.5)	48.8 (27.1)	51.8 (24.9)	54.3 (27.2)
24 hours post-dose	42.4 (22.4)	40.2 (29.3)	41.4 (28.9)	42.0 (27.9)
48 hours post-dose	36.6 (24.2)	42.4 (30.0)	33.9 (28.6)	32.4 (28.3)
72 hours post-dose	31.8 (25.0)	36.2 (27.6)	24.8 (24.3)	24.5 (26.8)
4 days post-dose	29.5 (24.8)	30.0 (23.4)	23.1 (26.0)	19.7 (24.4)
5 days post-dose	29.0 (24.8)	30.6 (26.4)	20.7 (24.5)	16.9 (24.5)
6 days post-dose	29.9 (23.7)	30.9 (25.2)	15.7 (26.7)	15.9 (24.1)
7 days post-dose	28.9 (26.0)	25.0 (24.6)	14.4 (20.0)	15.5 (24.4)

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

New flare compared to baseline flare: Clinical response based on patient's global assessment of response to treatment (Likert scale) in patients who were re-treated (Full Analysis Set)

	ACZ885 150 mg s.c. N=25		Triam 40 mg i.m. N=46	
Assessment / Time point	Baseline flare	New flare	Baseline flare	New flare
Patient's global assessment of response to treatment: excellent or good				
72 hours post-dose	12 / 20 (60.0)	11 / 20 (55.0)	23 / 39 (59.0)	23 / 39 (59.0)
7 days post-dose	14 / 22 (63.6)	15 / 22 (68.2)	30 / 41 (73.2)	26 / 41 (63.4)

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

New flare compared to baseline flare: Clinical response based on physician's global assessment of response to treatment (Likert scale) in patients who were re-treated (Full Analysis Set)

	ACZ885 150 mg s.c. N=25		Triam 40 mg i.m. N=46	
Assessment / Time point	Baseline flare	New flare	Baseline flare	New flare
Physician's global assessment of response to treatment: very good or good				
72 hours post-dose	19 / 23 (82.6)	17 / 23 (73.9)	25 / 41 (61.0)	30 / 41 (73.2)

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

New flare compared to baseline flare: Clinical response based on physician's assessment of tenderness and swelling in patients who were re-treated (Full Analysis Set)

	ACZ885 150 mg s.c. N=25		Triam 40 mg i.m. N=46	
Assessment / Time point	**Baseline flare**	**New flare**	**Baseline flare**	**New flare**
Physician's assessment of joint tenderness: no pain				
Baseline	1 / 25 (4.0)	0 / 25	0 / 46	0 / 46
72 hours post-dose	10 / 23 (43.5)	11 / 23 (47.8)	16 / 41 (39.0)	19 / 41 (46.3)
7 days post-dose	15 / 25 (60.0)	16 / 25 (64.0)	25 / 43 (58.1)	30 / 43 (69.8)
Physician's assessment of joint swelling: no swelling				
Baseline	1 / 25 (4.0)	0 / 25	1 / 46 (2.2)	2 / 46 (4.3)
72 hours post-dose	8 / 23 (34.8)	14 / 23 (60.9)	13 / 41 (31.7)	20 / 41 (48.8)
7 days post-dose	16 / 25 (64.0)	17 / 25 (68.0)	26 / 43 (60.5)	32 / 43 (74.4)

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

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	All Canakinumab	Canakinumab : Before Retreatment	Canakinumab : After Retreatment	All Triamcinolone Acetonide	Triam: Before Switch to Canakinumab	Triam: After Switch to Canakinumab
Total, serious adverse events						
# participants affected / at risk	12/112 (10.71 %)	1/62 (1.61%)	5/62 (8.06%)	4/114 (3.51%)	0/41 (0.00%)	3/41 (7.32%)
Blood and lymphatic system disorders						
Anaemia † [1]						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	1/41 (2.44%)
Haemorrhagic anaemia † [1]						

# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	1/41 (2.44%)
Cardiac disorders						
Angina pectoris † [1]						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	1/62 (1.61%)	0/114 (0.00%)	0/41 (0.00%)	1/41 (2.44%)
Aortic valve incompetence † [1]						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
Atrial fibrillation † [1]						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Cardiomyopathy † [1]						

# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
Congenital, familial and genetic disorders						
Bicuspid aortic valve † [1]						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
Gastrointestinal disorders						
Diarrhoea † [1]						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
Lower gastrointestinal haemorrhage † [1]						

# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	1/41 (2.44%)
Nausea † [1]						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
Pancreatitis † [1]						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Vomiting † [1]						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
General disorders						
Cyst † [1]						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Infections and infestations						

Abscess limb † [1]						
# participants affected / at risk	2/112 (1.79%)	1/62 (1.61%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Gastroenteritis † [1]						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Metabolism and nutrition disorders						
Diabetes mellitus † [1]						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	1/62 (1.61%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Musculoskeletal and connective tissue disorders						
Back pain † [1]						

# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Intervertebral disc protrusion † 1						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Prostate cancer † 1						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
Squamous cell carcinoma † 1						

# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	1/62 (1.61%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Nervous system disorders						
Cerebrovascular accident † 1						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Convulsion † 1						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	1/62 (1.61%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Haemorrhage intracranial † 1						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Trigeminal neuralgia † 1						

# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	1/62 (1.61%)	0/114 (0.00%)	0/41 (0.00%)	0/41 (0.00%)
Psychiatric disorders						
Alcohol withdrawal syndrome † 1						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)
Renal and urinary disorders						
Acute prerenal failure † 1						
# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	0/114 (0.00%)	0/41 (0.00%)	1/41 (2.44%)
Vascular disorders						
Aortic stenosis † 1						

# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	1/114 (0.88%)	0/41 (0.00%)	0/41 (0.00%)

† Events were collected by systematic assessment

1 Term from vocabulary, MedDRA

Other Adverse Events by System Organ Class

Threshold above which other adverse events are reported - 5**%**

	All Canakinumab	Canakinumab : Before Retreatment	Canakinumab : After Retreatment	All Triamcinolone Acetonide	Triam: Before Switch to Canakinumab	Triam: After Switch to Canakinumab
Total, other (not including serious) adverse events						
# participants affected / at risk	42/112 (37.50 %)	15/62 (24.19 %)	19/62 (30.65 %)	36/114 (31.58 %)	15/41 (36.59 %)	8/41 (19.51 %)
Gastrointestinal disorders						
Nausea † [1]						
# participants affected / at risk	3/112 (2.68%)	2/62 (3.23%)	1/62 (1.61%)	3/114 (2.63%)	1/41 (2.44%)	3/41 (7.32%)
Infections and infestations						
Nasopharyngitis † [1]						

# participants affected / at risk	0/112 (0.00%)	0/62 (0.00%)	0/62 (0.00%)	5/114 (4.39%)	4/41 (9.76%)	2/41 (4.88%)
Upper respiratory tract infection † [1]						
# participants affected / at risk	9/112 (8.04%)	4/62 (6.45%)	7/62 (11.29%)	3/114 (2.63%)	1/41 (2.44%)	1/41 (2.44%)
Injury, poisoning and procedural complications						
Muscle strain † [1]						
# participants affected / at risk	1/112 (0.89%)	0/62 (0.00%)	0/62 (0.00%)	3/114 (2.63%)	3/41 (7.32%)	3/41 (7.32%)
Musculoskeletal and connective tissue disorders						

Arthralgia † [1]						
# participants affected / at risk	8/112 (7.14%)	1/62 (1.61%)	5/62 (8.06%)	10/114 (8.77%)	3/41 (7.32%)	2/41 (4.88%)
Back pain † [1]						
# participants affected / at risk	12/112 (10.71%)	2/62 (3.23%)	6/62 (9.68%)	2/114 (1.75%)	1/41 (2.44%)	0/41 (0.00%)
Muscle spasms † [1]						
# participants affected / at risk	4/112 (3.57%)	2/62 (3.23%)	1/62 (1.61%)	7/114 (6.14%)	4/41 (9.76%)	0/41 (0.00%)
Pain in extremity † [1]						
# participants affected / at risk	2/112 (1.79%)	1/62 (1.61%)	0/62 (0.00%)	6/114 (5.26%)	4/41 (9.76%)	1/41 (2.44%)
Nervous system disorders						
Headache † [1]						

# participants affected / at risk	5/112 (4.46%)	3/62 (4.84%)	2/62 (3.23%)	6/114 (5.26%)	2/41 (4.88%)	1/41 (2.44%)
Vascular disorders						
Hypertension † [1]						
# participants affected / at risk	14/112 (12.50 %)	3/62 (4.84%)	7/62 (11.29%)	7/114 (6.14%)	2/41 (4.88%)	1/41 (2.44%)

† Events were collected by systematic assessment

1 Term from vocabulary, MedDRA

Date of Clinical Trial Report

03-Jul-2012