Sponsor

Novartis Pharmaceuticals, E. Hanover

Generic Drug Name

Canakinumab (ACZ885)

Therapeutic Area of Trial

Rheumatoid arthritis

Approved Indication

Investigational

Study Number

CACZ885A2201E1, CACZ885A2201E2

Title

Extension studies to evaluate the efficacy, safety and tolerability of canakinumab (ACZ885 an anti-interleukin-1β monoclonal antibody) in patients with active rheumatoid arthritis

Phase of Development

Phase II

Study Start/End Dates

Study Initiation Dates:

CACZ885A2201E1: 18-Apr-2007 (first patient first visit);

CACZ885A2201E2: 16-Oct-2008 (first patient first visit)

Study Completion Dates:

CACZ885A2201E1: 19-Oct-2009 (last patient last visit);

CACZ885A2201E2: 04-Aug-2009 (last patient last visit)

Early Termination Date:

15-Jun-2009 (for both studies)

Study Design/Methodology

Both extension studies were multi-center, open-label, non-randomized trials without a comparator. The first extension study, CACZ885A2201E1, extended active treatment by 76 weeks to those patients who had completed the core study [CACZ885A2201]. The second extension study, CACZ885A2201E2, further extended active treatment by 96 weeks for those patients who had completed the first extension study.

Outline of core and extension studies

Core Study: [CACZ885A2201]	Extension 1: CACZ885A2201E1	Extension 2: CACZ885A2201E2
12 Weeks double-blind treatment	76 Weeks open-label treatment	2 Years open-label treatment
Visits 1-12 (V13+V14 follow-up)	Visits 12-31 (V32+V33 follow-up)	Visits 31-57 (V58 follow-up)
•600 mg i.v. loading dose + 300 mg s.c. q2wk •300 mg s.c. q2wk •150 mg s.c. q4wk •Placebo q2wk	•300/150 mg s.c. q4wk or •300/150 mg s.c. q2wk for incomplete responder patients Note: All patients started on 300 mg and later during the study the dose was lowered to 150 mg by a protocol amendment	•300/150 mg s.c. q4wk or •300/150 mg s.c. q2wk for incomplete responder patients Note: After the study start, the dose was lowered from 300 mg to 150 mg by a protocol amendment

s.c-subcutaneous; i.v.- intravenous;q2/4week-every 2/4 week,

Dosing in the extension studies is according to randomization in the core study

- Patients who were exposed to one of 3 active treatment arms, ACZ885 600 mg i.v. loading dose plus 300 mg s.c. q2wk, ACZ885 300 mg s.c. q2wk or ACZ885 150 mg s.c. q4wk in the core study [CACZ885A2201] and completed the study, up to and including Visit 12, were to continue in the extension study on 150 mg ACZ885 s.c. q4wk (with the possibility of dose titration)
- Patients who were exposed to placebo in the core study [CACZ885A2201] and completed the study, up to and including Visit 12, were to continue in the extension 1 study on 300 mg ACZ885 s.c. q4wk (with the possibility of dose titration)
- The ACZ885 dose was lowered from 300 mg to 150 mg by a protocol amendment (Amendment 3 for CACZ8852201E1) which was introduced approximately 21 months after first patient first visit

At Visit 13 (16-week visit), patients who had not improved according to the ACR20 measures and criteria of response were to be up-titrated to a dose regimen of 300 mg ACZ885 q2wk. If improvement according to the ACR 20 criteria was still not observed after two months in extension 1 study (Visit 14), the patient was to be discontinued from the study in order to avoid extended treatment with canakinumab.

Extension 2

Upon completion of the first extension study, CACZ885A2201E1, patients had the option of continuing active treatment for an additional 96 weeks. The ACZ885 dose was lowered from 300 mg to 150 mg by a protocol amendment approximately 3 months after first patient first visit

The End of Study (EoS) visit (Visit 31) of extension 1 study was the planned first visit of extension 2 study. Patients who were rolling over to extension 2 study did not need to perform visits 32 and 33 of extension 1 study. However, patients who did not join extension 2 had to continue to follow the visit schedule of extension 1 study including Visits 32 and 33.

Centres

For CACZ885A2201E1 – Austria (3 centers), Belgium (1), Canada (8), Germany (10), Spain (6), and U.S. (13).

For CACZ885A2201E2 – Austria (1), Belgium (1), Canada (3), Germany (7), Spain (2), and U.S. (3).

Publication

NA

Objectives

Primary objective(s)

The primary objective of the extension studies was to:

- assess long-term safety and tolerability of canakinumab (ACZ885) in patients with active RA. CACZ885A2201E1 evaluated this objective in patients who had participated in the core study (CACZ885A2201) and CACZ885A2201E2 did the same in patients who completed the first extension study.

Secondary objective(s)

The secondary objectives of the extension studies were:

- to evaluate the efficacy of canakinumab according to American College of Rheumatology(ACR) criteria; ACR20, ACR50 and ACR70 criteria, DAS28, and ACR components including hsCRP (a marker of inflammation).
- The immunogenicity and pharmacokinetic profile of canakinumab were assessed

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

Canakinumab (ACZ885) was supplied in individual 6 mL glass vials containing 150 mg canakinumab as a lyophilized cake. For administration of the 300 mg dose, patients received two s.c. injections of 150 mg ACZ885.

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

NA

Criteria for Evaluation

Primary variables

- The primary efficacy variable was the response to treatment according to ACR50, ACR20 and ACR70 criteria and to DAS28

Secondary variables

- The secondary efficacy objectives were to assess the effect of ACZ885 on ACR components, including a marker of inflammation (hsCRP).ACR components assessed were :
  - swollen 28-joint count,
  - tender 28-joint count,
  - patient's pain intensity,
  - patient's global assessment of disease activity,
  - physician's global assessment of disease activity,
  - Health Assessment Questionnaire (HAQ©)score, and
  - hsCRP,
- Distinct response to treatment according to ACR20, ACR50 and ACR70 criteria, EULAR response, and ESR level.

Safety and tolerability

Evaluation of safety included:

- analyses of adverse events (AEs), including serious adverse events (SAEs), standard clinical laboratory parameters, vital signs, ECGs and local tolerability at the injection site

Pharmacology

- The PK parameters (AUC_{τ}, C_{max}, and T_{max}) were determined in plasma using non-compartmental methods.

Other

Immunogenicity assessment was listed along with date, scheduled time point and actual time of sample collection.

Statistical Methods

Data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and pharmacokinetic measurements.

All summaries of categorical data were presented as frequencies and percentages.

All summaries of continuous data presented mean, median, standard deviation, minimum and maximum and the number of non-missing data points.

Efficacy data were analyzed using the ITT population and safety data using the safety population. All tables and listings were presented according to the randomization assignment in the core study (CACZ885A2201), with the change to display always the total and to join the core study treatment groups ACZ885 600 mg i.v. loading dose plus 300 mg s.c. q2wk and ACZ885 300 mg s.c. q2wk.

Study Population: Inclusion/Exclusion Criteria and Demographics

Study Population:

For both extension studies, the study population consisted of adult (male and non-pregnant, non-lactating female) patients of at least 18 years of age with active RA as defined by the American College of Rheumatology (ACR) Criteria for the Classification of Rheumatoid Arthritis who had completed the core study [CACZ885A2201].

Inclusion Criteria

- Patients were included in extension 1 study if they had completed the core study [CACZ885A2201] and signed the informed consent form. A patient was defined as having completed the core study if he/she completed the study up to and including Visit 12.
- Patients were included in extension 2 study if they had completed the first extension study-CACZ885A2201E1 and signed the informed consent form. A patient was defined as having completed the first extension study if he/she completed the study up to and including Visit 31.

Exclusion Criteria

Patients were excluded from extension 1 study if they met any of the following criteria:

- Patients whose continued treatment in extension 1 study was not considered appropriate by the treating physician.
- Patients who were non-compliant or who demonstrated a major protocol violation in the core study [CACZ885A2201].
- Patients who discontinued from the core study [CACZ885A2201] before Visit 12.

Patients were excluded from extension 2 study if they met any of the following criteria:

- Patients for whom continuation of treatment in extension 2 study was not considered appropriate by the treating physician.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation confirmed by a positive hCG laboratory test (>5mIU/mL).
- Women of childbearing potential (WOCBP) defined as all women physiologically capable of becoming pregnant, unless they were:
  - Using a double barrier method of contraception such as intrauterine devices (IUDs), oral contraceptives, sub-dermal implants and a barrier method with spermicide, condoms.
  - Women whose partners have been sterilized by vasectomy or other means.
  - Considered post-menopausal and not of childbearing potential if they have had 24 months

of natural (spontaneous) amenorrhea or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL (for US only estradiol < 20 pg/mL) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Note: FSH and estradiol tests did not need to be performed for surgically sterile or women on estrogen replacement therapy.

Females of childbearing potential had to agree to continue to practice an acceptable form of birth control during the trial and for at least 2 months after completing the trial.

Number of Subjects

Patient disposition (Safety population)

Total number of patients studied	ACZ885 300 mg sc q2wk N=110 n (%)	ACZ885 150 mg sc q4wk N=59 n (%)	Placebo N=58 n (%)	Total N=227 n (%)
Completed	8 (7.3)	4 (6.8)	3 (5.2)	15 (6.6)
Discontinued	102 (92.7)	55 (93.2)	55 (94.8)	212 (93.4)
Adverse Event(s)	9 (8.2)	5 (8.5)	4 (6.9)	18 (7.9)
Unsatisfactory therapeutic effect	16 (14.5)	14 (23.7)	11 (19.0)	41 (18.1)
Subject withdrew consent	5 (4.5)	3 (5.1)	4 (6.9)	12 (5.3)
Lost to follow-up	2 (1.8)	0	0	2 (0.9)
Administrative problems	69 (62.7)	32 (54.2)	35 (60.3)	136 (59.9)
Death	0	0	1 (1.7)	1 (0.4)
Protocol deviation	1 (0.9)	1 (1.7)	0	2 (0.9)

Dosing in the extension studies is according to randomization in the core study

Demographic and Background Characteristics

Variable	ACZ885 300 mg sc q2wk N=110	ACZ885 150 mg sc q4wk N=59	Placebo N=58	Total N=227
Baseline age – n (%)				
≥18 - < 41	7 (6.4)	6 (10.2)	6 (10.3)	19 (8.4)
≥ 41 - < 65	66 (60.0)	39 (66.1)	38 (65.5)	143 (63.0)
≥ 65 - < 75	25 (22.7)	12 (20.3)	12 (20.7)	49 (21.6)
≥ 75	12 (10.9)	2 (3.4)	2 (3.4)	16 (7.0)
Baseline age (years)				
n	110	59	58	227
Mean	58.26	56.42	56.62	57.37
SD	12.005	10.830	11.882	11.661
Median	59.00	57.00	56.50	58.00
Min	32.0	32.0	29.0	29.0
Max	82.0	79.0	85.0	85.0
Sex – n (%)				
Female	94 (85.5)	47 (79.7)	44 (75.9)	185 (81.5)
Male	16 (14.5)	12 (20.3)	14 (24.1)	42 (18.5)
Predominant race – n (%)				
Asian	2 (1.8)	0	0	2 (0.9)
Black	1 (0.9)	1 (1.7)	1 (1.7)	3 (1.3)
Caucasian	102 (92.7)	58 (98.3)	56 (96.6)	216 (95.2)
Native American	1 (0.9)	0	0	1 (0.4)
Other	3 (2.7)	0	1 (1.7)	4 (1.8)
Pacific islander	1 (0.9)	0	0	1 (0.4)
Ethnicity – n (%)				
Hispanic/Latino	5 (4.5)	2 (3.4)	3 (5.2)	10 (4.4)
Indian (Indian subcontinent)	1 (0.9)	0	0	1 (0.4)
Other	104 (94.5)	57 (96.6)	55 (94.8)	216 (95.2)
Duration of RA (years)				
n	110	59	58	227
Mean	9.61	10.82	9.11	9.80
SD	7.885	9.694	9.334	8.746
Median	8.05	8.50	5.95	7.60
Min	0.3	0.5	0.6	0.3
Max	38.9	46.5	45.1	46.5
Number of prior DMARDS [1] – n (%)				
0	81 (73.6)	43 (72.9)	46 (79.3)	170 (74.9)
1	23 (20.9)	13 (22.0)	10 (17.2)	46 (20.3)
2	4 (3.6)	2 (3.4)	2 (3.4)	8 (3.5)
3	2 (1.8)	1 (1.7)	0	3 (1.3)
Functional status (ACR				

1991) - n (%)				
Class I	9(8.2)	4(6.8)	0(0.0)	13(5.7)
Class II	73(66.4)	44(74.6)	42(72.4)	159(70.0)
Class III	27(24.5)	11(18.6)	16(27.6)	54(23.8)
Class IV	1(0.9)	0	0	1(0.4)
Height (cm)				
n	110	59	58	227
Mean	163.21	165.73	165.22	164.38
SD	7.462	8.491	7.970	7.919
Median	163.00	167.00	164.00	164.00
Min	148.0	147.0	146.0	146.0
Max	190.0	188.0	183.0	190.0
Weight (kg)				
n	110	59	58	227
Mean	73.47	76.42	76.41	74.99
SD	13.287	14.218	13.608	13.635
Median	73.80	73.50	75.10	74.00
Min	48.0	49.5	47.3	47.3
Max	106.0	109.5	106.8	109.5
Body mass index (BMI) (kg/m2)				
n	110	59	58	227
Mean	27.55	27.74	27.97	27.71
SD	4.432	4.098	4.455	4.338
Median	27.70	26.91	27.90	27.59
Min	17.7	18.2	18.6	17.7
Max	41.0	33.9	34.0	41.0

[1] Only DMARDs other than MTX are considered

Dosing in the extension studies is according to randomization in the core study

Primary Objective Result(s)

Number (%) of ACR20-ACR50-ACR70 responders by visit (ITT population)

Time point Response	ACZ885 300 mg sc q2wk n/N (%)	ACZ885 150 mg sc q4wk n/N (%)	Placebo n/N (%)	Total n/N (%)
End of core study / Week 12				
ACR20	54/109 (49.5)	28/58 (48.3)	17/58 (29.3)	99/225 (44.0)
ACR50	22/109 (20.2)	16/58 (27.6)	6/58 (10.3)	44/225 (19.6)
ACR70	5/110 (4.5)	4/59 (6.8)	1/58 (1.7)	10/227 (4.4)
Visit 15 / Week 24				
ACR20	55/105 (52.4)	37/57 (64.9)	37/56 (66.1)	129/218 (59.2)
ACR50	20/106 (18.9)	17/57 (29.8)	21/56 (37.5)	58/219 (26.5)
ACR70	6/106 (5.7)	6/57 (10.5)	8/56 (14.3)	20/219 (9.1)
Visit 18 / Week 36				
ACR20	57/100 (57.0)	32/48 (66.7)	31/49 (63.3)	120/197 (60.9)
ACR50	24/100 (24.0)	15/48 (31.3)	16/49 (32.7)	55/197 (27.9)
ACR70	7/100 (7.0)	2/48 (4.2)	6/49 (12.2)	15/197 (7.6)
Visit 21/ Week 48				
ACR20	63/95 (66.3)	35/43 (81.4)	34/47 (72.3)	132/185 (71.4)
ACR50	33/95 (34.7)	21/43 (48.8)	16/47 (34.0)	70/185 (37.8)
ACR70	10/96 (10.4)	4/43 (9.3)	3/47 (6.4)	17/186 (9.1)
Visit 24 / Week 60				
ACR20	53/87 (60.9)	30/40 (75.0)	31/42 (73.8)	114/169 (67.5)
ACR50	30/87 (34.5)	17/40 (42.5)	18/42 (42.9)	65/169 (38.5)
ACR70	14/87 (16.1)	7/40 (17.5)	8/42 (19.0)	29/169 (17.2)
Visit 27 / Week 72				
ACR20	41/66 (62.1)	26/34 (76.5)	20/27 (74.1)	87/127 (68.5)
ACR50	25/66 (37.9)	20/34 (58.8)	13/27 (48.1)	58/127 (45.7)
ACR70	10/66 (15.2)	7/34 (20.6)	4/27 (14.8)	21/127 (16.5)
Visit 31 / Week 88				
ACR20	29/43 (67.4)	18/25 (72.0)	19/23 (82.6)	66/91 (72.5)
ACR50	17/43 (39.5)	11/25 (44.0)	12/23 (52.2)	40/91 (44.0)
ACR70	7/44 (15.9)	4/25 (16.0)	4/23 (17.4)	15/92 (16.3)
Visit 36 / Week 100				
ACR20	17/21 (81.0)	9/12 (75.0)	11/14 (91.7)	37/47 (78.7)
ACR50	10/21 (47.6)	4/13 (30.8)	8/14 (57.1)	22/48 (45.8)
ACR70	3/21 (14.3)	3/14 (21.4)	4/14 (28.6)	10/49 (20.4)
Visit 39 / Week 112				
ACR20	10/13 (76.9)	6/8 (75.0)	4/6 (66.7)	20/27 (74.1)
ACR50	3/13 (23.1)	5/8 (62.5)	4/6 (66.7)	12/27 (44.4)
ACR70	1/13 (7.7)	3/8 (37.5)	2/6 (33.3)	6/27 (22.2)
Visit 42 / Week 124				
ACR20	2/2 (100.0)	1/1 (100.0)	1/1 (100.0)	4/4 (100.0)
ACR50	1/2 (50.0)	1/1 (100.0)	1/1 (100.0)	3/4 (75.0)
ACR70	1/2 (50.0)	1/1 (100.0)	0/1 (0.0)	2/4 (50.0)

End of study visit				
ACR20	53/103 (51.5)	29/53 (54.7)	33/54 (61.1)	115/210 (54.8)
ACR50	24/103 (23.3)	19/53 (35.8)	19/54 (35.2)	62/210 (29.5)
ACR70	14/103 (13.6)	9/54 (16.7)	7/54 (13.0)	30/211 (14.2)

n: Number of subjects who are at the corresponding category
N: The total number of subjects in the treatment group
Dosing in the extension studies is according to randomization in the core study

Number of distinct responders according to ACR20, ACR50 and ACR70 criteria at end of study (ITT population)

Response	ACZ885 300 mg sc q2wk N=110 n (%)	ACZ885 150 mg sc q4wk N=59 n (%)	Placebo N=58 n (%)	Total N=227 n (%)
No response	50 (45.5)	24 (40.7)	21 (36.2)	95 (41.9)
ACR20 – not ACR50	29 (26.4)	10 (16.9)	14 (24.1)	53 (23.3)
ACR50 – not ACR70	10 (9.1)	10 (16.9)	12 (20.7)	32 (14.1)
ACR70	14 (12.7)	9 (15.3)	7 (12.1)	30 (13.2)

The number of patients achieving the ACR20 criterion is the sum of the last 3 rows
The number of patients achieving the ACR50 criterion is the sum of the last 2 rows
The number of patients achieving the ACR70 criterion is the last row
Dosing in the extension studies is according to randomization in the core study

DAS28: summary statistics and change from baseline (ITT population)

Timepoint Statistics	ACZ885 300 mg sc q2wk N=110	ACZ885 150 mg sc q4wk N=59	Placebo N=58	Total N=224
End of core study / Week 12				
n	108	58	58	224
Baseline – mean (SD)	5.81 (0.744)	5.77 (0.754)	5.78 (0.731)	5.79 (0.740)
Post-baseline – mean (SD)	4.44 (1.358)	4.30 (1.473)	4.92 (1.669)	4.53 (1.486)
Change from baseline – mean (SD)	-1.37 (1.175)	-1.47 (1.230)	-0.86 (1.392)	-1.26 (1.266)
Visit 15 / Week 24				
n	103	56	54	213
Baseline – mean (SD)	5.79 (0.691)	5.72 (0.702)	5.82 (0.727)	5.78 (0.701)
Post-baseline – mean (SD)	4.19 (1.288)	3.91 (1.493)	3.89 (1.552)	4.04 (1.414)
Change from baseline – mean (SD)	-1.60 (1.171)	-1.82 (1.333)	-1.93 (1.474)	-1.74 (1.298
Visit 27 / Week 72				
n	63	31	26	120
Baseline – mean (SD)	5.83 (0.676)	5.71 (0.585)	5.66 (0.682)	5.76 (0.653)

Time point Statistics	ACZ885 300 mg sc q2wk N=110	ACZ885 150 mg sc q4wk N=59	Placebo N=58	Total N=224
Post-baseline – mean (SD)	3.65 (1.371)	3.13 (1.160)	3.46 (1.239)	3.47 (1.300)
Change from baseline – mean (SD)	-2.18 (1.302)	-2.58 (1.232)	-2.21 (1.132)	-2.29 (1.251
Visit 39 / Week 112				
n	13	8	6	27
Baseline – mean (SD)	5.77 (0.479)	5.79 (0.534)	5.55 (0.796)	5.73 (0.560)
Post-baseline – mean (SD)	3.77 (0.850)	3.07 (1.219)	2.96 (1.398)	3.38 (1.121)
Change from baseline – mean (SD)	-2.00 (1.110)	-2.73 (1.252)	-2.59 (1.916)	-2.34 (1.347
End of study visit				
n	100	52	49	201
Baseline – mean (SD)	5.78 (0.754)	5.73 (0.712)	5.88 (0.730)	5.79 (0.736)
Post-baseline – mean (SD)	3.95 (1.424)	3.94 (1.656)	4.02 (1.566)	3.96 (1.514)
Change from baseline –	-1.83 (1.434)	-1.79 (1.551)	-1.86 (1.621)	-1.83 (1.504

Change from baseline = Post Baseline – Baseline
Baseline is defined as the value at Visit 3 from the core CACZ885A2201 study
At each timepoint, only patients with a value at both Baseline and that timepoint are included
Dosing in the extension studies is according to randomization in the core study

Secondary Objective Result(s)

Not available

Safety Results

Adverse Events by System Organ Class

Number (%) of patients with adverse events by primary system organ class (Safety population)

	ACZ885 300 mg sc q2wk N=110	ACZ885 150 mg sc q4wk N=59	Placebo N=58	Total N=227
Primary system organ class	**n (%)**	**n (%)**	**n (%)**	**n (%)**
n (%) of patients with any AE	86 (78.2)	47 (79.7)	43 (74.1)	176 (77.5)
Blood and lymphatic system disorders	3 (2.7)	1 (1.7)	1 (1.7)	5 (2.2)
Cardiac disorders	7 (6.4)	1 (1.7)	6 (10.3)	14 (6.2)
Ear and labyrinth disorders	6 (5.5)	1 (1.7)	2 (3.4)	9 (4.0)
Endocrine disorders	2 (1.8)	1 (1.7)	1 (1.7)	4 (1.8)
Eye disorders	8 (7.3)	1 (1.7)	3 (5.2)	12 (5.3)
Gastrointestinal disorders	33 (30.0)	15 (25.4)	10 (17.2)	58 (25.6)
General disorders and administration site conditions	15 (13.6)	5 (8.5)	10 (17.2)	30 (13.2)
Hepatobiliary disorders	0	1 (1.7)	0	1 (0.4)
Immune system disorders	2 (1.8)	0	1 (1.7)	3 (1.3)
Infections and infestations	57 (51.8)	22 (37.3)	22 (37.9)	101 (44.5)
Injury, poisoning and procedural complications	19 (17.3)	6 (10.2)	6 (10.3)	31 (13.7)
Investigations	11 (10.0)	4 (6.8)	5 (8.6)	20 (8.8)
Metabolism and nutrition disorders	3 (2.7)	1 (1.7)	3 (5.2)	7 (3.1)
Musculoskeletal and connective tissue disorders	44 (40.0)	24 (40.7)	14 (24.1)	82 (36.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (5.5)	2 (3.4)	1 (1.7)	9 (4.0)
Nervous system disorders	22 (20.0)	9 (15.3)	9 (15.5)	40 (17.6)
Psychiatric disorders	8 (7.3)	2 (3.4)	1 (1.7)	11 (4.8)
Renal and urinary disorders	4 (3.6)	4 (6.8)	2 (3.4)	10 (4.4)
Reproductive system and breast disorders	3 (2.7)	3 (5.1)	0	6 (2.6)
Respiratory, thoracic and mediastinal disorders	18 (16.4)	4 (6.8)	10 (17.2)	32 (14.1)
Skin and subcutaneous tissue disorders	12 (10.9)	9 (15.3)	6 (10.3)	27 (11.9)
Vascular disorders	14 (12.7)	4 (6.8)	2 (3.4)	20 (8.8)

AEs by primary system organ class are presented alphabetically. A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Dosing in the extension studies is according to randomization in the core study

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

Number (%) of patients with most frequent adverse events by preferred term (at least 2 % in any group) (Safety population)

	ACZ885	ACZ885		
	300 mg sc q2wk N=110	150 mg sc q4wk N=59	Placebo N=58	Total N=227
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Nasopharyngitis	19 (17.3)	10 (16.9)	7 (12.1)	36 (15.9)
Rheumatoid arthritis	9 (8.2)	6 (10.2)	5 (8.6)	20 (8.8)
Upper respiratory tract infection	9 (8.2)	2 (3.4)	6 (10.3)	17 (7.5)
Arthralgia	8 (7.3)	5 (8.5)	3 (5.2)	16 (7.0)
Urinary tract infection	9 (8.2)	3 (5.1)	4 (6.9)	16 (7.0)
Bronchitis	9 (8.2)	4 (6.8)	2 (3.4)	15 (6.6)
Headache	7 (6.4)	4 (6.8)	3 (5.2)	14 (6.2)
Diarrhea	9 (8.2)	3 (5.1)	1 (1.7)	13 (5.7)
Cough	5 (4.5)	2 (3.4)	5 (8.6)	12 (5.3)
Hypertension	7 (6.4)	4 (6.8)	0	11 (4.8)

AEs preferred terms in each primary system organ class are presented in the order of descending frequency of the Total column

Dosing in the extension studies is according to randomization in the core study

Serious Adverse Events and Deaths

Deaths, non-fatal SAEs and other significant AEs (Safety population)

	ACZ885 300 mg sc q2wk N=110	ACZ885 150 mg sc q4wk N=59	Placebo N=58	Total N=227
	n (%)	**n (%)**	**n (%)**	**n (%)**
Death	0	0	1 (1.7)	1 (0.4)
Non-fatal SAEs	22 (20.0)	11 (18.6)	11 (19.0)	44 (19.4)
AEs causing temporary interruption of study drug	14 (12.7)	9 (15.3)	8 (13.8)	31 (13.7)
Infection AEs according to investigator's opinion	61 (55.5)	22 (37.3)	27 (46.6)	110 (48.5)
Discontinuation due to				
Any AEs including SAEs	9 (8.2)	5 (8.5)	4 (6.9)	18 (7.9)
SAEs (fatal and non fatal)	3 (2.7)	2 (3.4)	2 (3.4)	7 (3.1)
AEs (non-serious)	6 (5.5)	3 (5.1)	3 (5.2)	12 (5.3)

Counts are not mutually exclusive; patients may have had events which fall into more than one category. Data regarding the number of patients who died and the number of any AEs including SAEs leading to discontinuation are collected from the study completion page. All other information is collected from the AE page

Dosing in the extension studies is according to randomization in the core study

Other Relevant Findings

ACZ885 showed no immunogenicity. The PK parameters of ACZ885 were typical of a human IgG1-type antibody, with low volume of distribution and slow systemic clearance.

Date of Clinical Trial Report

06-May-2010

Date Inclusion on Novartis Clinical Trial Results Database

06-September-10

Date of Latest Update

31-August-10