Sponsor

Novartis

Generic Drug Name

Canakinumab (ACZ885)

Trial Indication

Rheumatoid Arthritis

Protocol Number

CACZ885A2211

Protocol Title

A 54-week, phase II, multi-center, open-label extension study to evaluate the efficacy, safety and tolerability of ACZ885 (anti-interleukin-1β monoclonal antibody) in patients with rheumatoid arthritis

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

11-Oct-2007 to 13-Aug-2009

Reason for Termination

Novartis terminated the study based on a project level decision to stop the development of ACZ885 in rheumatoid arthritis (RA) indication.

Study Design/Methodology

Multi-center, open-label, uncontrolled, non-randomized 54-week extension study to the core studies CACZ885A2204, CACZ885A2206 and CACZ885A2207 to assess the long-term safety and tolerability of ACZ885, long-term efficacy through ACR, SDAI and DAS28 scoring, long-term preservation and/or improvement of joint structure and bone mineral density (in CACZ885A2204 completer patients), as well as long term maintenance of health-related quality of life, in patients with RA who completed the treatment period of one of the core studies.

Centers

29 centres in 9 countries: Germany (5), Turkey (3), Spain (3), Russia (3), Italy (1), Belgium (2), United States of America (8), Netherlands (3), and Switzerland (1).

Objectives:

Primary objective

To assess the long-term safety and tolerability (and in particular the infection occurrence) of ACZ885 in patients with RA who participated in the core CACZ885A2204, CACZ885A2206, or CACZ885A2207 studies.

Secondary objectives

- To evaluate the efficacy of ACZ885 by assessing the time course of the response to treatment according to American College of Rheumatology (ACR)20, ACR50, ACR70, and ACR90 criteria, and by using the Simplified Disease Activity Index (SDAI) and Disease Activity Score 28 (DAS28).
- To assess the effect of ACZ885 on ACR components, including a marker of inflammation (C- reactive protein).
- To characterize the magnitude of ACZ885 joint structure preservation and/or improvement using magnetic resonance imaging (MRI) in RA patients who participated in the core study CACZ885A2204 and had completed baseline and 26 weeks assessments.
- To evaluate the effect of ACZ885 treatment on radiographically detectable change in joint structure (hands and feet) using change in modified Sharp/van der Heijde score in RA patients who participated in the core study CACZ885A2204 and had completed baseline and 26 weeks assessments.
- To characterize the magnitude of ACZ885 stabilization and/or improvement of the bone mineral density (BMD) of the hand using dual-energy X-ray absorptiometry (DXA) in RA patients who participated in the core study CACZ885A2204 and had completed baseline and 26 weeks assessments.

- To assess the long-term immunogenicity of ACZ885.
- To evaluate the long-term pharmacokinetics (PK) of ACZ885.
- To assess the long term maintenance of health-related quality of life (HRQoL) by using the Medical Outcome Short Form (36) Health Survey (SF-36®).

Test Product, Dose, and Mode of Administration

ACZ885 (canakinumab) 150 mg lyophilized cake for reconstitution of solution for intravenous infusion (i.v.).

One single dose of 600 mg i.v. on Day 1 and from then on every 6 weeks (± 5 days), for a total planned treatment period of 54 weeks.

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

Not applicable.

Criteria for Evaluation

Primary variables: Safety and tolerability

Safety and tolerability of ACZ885 as assessed by:

- Adverse events (AEs), with particular focus on occurrence of infections; serious adverse events (SAEs), with their severity and relationship to study drug; and pregnancies.
- Regular monitoring of hematology, blood chemistry, and urine (performed by a central laboratory).
- Regular assessments of vital signs, 12-lead ECG, physical condition and body weight.

Secondary variables

- Clinical response to treatment (ACR 20, 50, 70, 90), assessed at each visit.
- SDAI and DAS28, assessed at each visit.
- Magnetic resonance imaging (MRI) of the most swollen wrist (determined at baseline by the investigator site), performed at Week 18 (± 1 week) using a whole body MRI system with image acquisition according to the OMERACT recommendation (applicable only for patients who completed the core study CACZ885A2204).
- Bone mineral density, measured at Week 18 (± 1 week) by DXA of the hand with the most swollen wrist (determined at baseline by the investigator site), lumbosacral (LS) spine and hip (applicable only for patients who completed the core study CACZ885A2204).
- Evaluation of radiographic bone erosions (numeric count), modified Sharp/van der Heijde score from digital radiographic (X-ray) assessment of both hands and both feet, performed at Week 18 (± 1 week) (applicable only for patients who completed the core study CACZ885A2204).
- Change in HRQoL assessed at baseline and every 12 weeks using HAQ® and SF-36® questionnaires.

- Immunogenicity: measurement of anti-ACZ885 antibodies.

Pharmacokinetics
Canakinumab concentrations in serum by competitive enzyme linked immunosorbent assay (ELISA).

Pharmacodynamics

Total interleukin 1beta (IL-1β) in serum by ELISA.

Other – Special clinical laboratory evaluations
- Antinuclear antibodies (ANA)
- Bone markers: C-terminal cross-linking telopeptide of type I collagen (CTX-I) in serum, C-terminal cross-linking telopeptide of type II collagen (CTX-II) in urine, and glucosyl- galactosyl-pyridinoline (Glc-Gal-PYD) in urine.
- Rheumatoid factor (RF)
- Anti-cyclic citrullinated peptide antibodies (anti-CCP)

Statistical Methods

No statistical analyses were performed.

Depending on the type of data, different groupings were used to summarize the data. The following groupings were used:
- Across all subjects.
- Grouped by whether or not the subject received ACZ885 treatment in the core trial.
- Grouped by core trial.
- Grouped by core trial and whether or not the subject received ACZ885 treatment in the core trial.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion criteria

Patients (male and non-pregnant, non-lactating females) who completed the core CACZ885A2204, CACZ885A2206 or CACZ885A2207 study without serious or severe drug- related adverse effects could enter the extension study upon signing informed consent.

Key Exclusion criteria

- Patients for whom continued treatment in the extension is not considered appropriate by the treating physician.
- Patients who were non-compliant or who demonstrated a major protocol violation in the core study.
- Patients who did not complete / discontinued from the core study.
- Patients with drug related SAEs or severe adverse events.

Participant Flow Table

Patient disposition – n (%) of subjects (Safety analysis set)

	Total N=115	2204 N=56	2206 N=8	2207 N=51
Patients				
Completed	30 (26%)	23 (41%)	3 (38%)	4 (8%)
Discontinued	85 (74%)	33 (59%)	5 (63%)	47 (92%)
Main cause of discontinuation				
Adverse Event(s)	3 (3%)	0	1 (13%)	2 (4%)
Abnormal laboratory value(s)	1 (1%)	0	0	1 (2%)
Unsatisfactory therapeutic effect	14 (12%)	3 (5%)	1 (13%)	10 (20%)
Subject withdrew consent	2 (2%)	0	0	2 (4%)
Lost to follow-up	2 (2%)	2 (4%)	0	0
Administrative problems*	60 (52%)	26 (46%)	3 (38%)	31 (61%)
Death	1 (1%)	0	0	1 (2%)
Protocol deviation	2 (2%)	2 (4%)	0	0

*'Administrative problems' was stated as the reason for discontinuation for subjects who were still ongoing in the study at the time of study termination

Baseline Characteristics

Demographic summary (Safety analysis set)

		Total N=115
Age (years)	Mean (SD)	52.3 (13.16)
	Median	52.0
	Range	19 - 74
Gender - n(%)	Male	22 (19.1 %)
	Female	93 (80.9 %)
Race - n(%)	Caucasian	109 (94.8 %)
	Black	2 (1.7 %)
	Asian	2 (1.7 %)
	Native American	1 (0.9 %)
	Other	1 (0.9 %)
Ethnicity - n(%)	Hispanic/Latino	12 (10.4 %)
	Other	103 (89.6 %)

Primary Outcome Results(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Results

Clinical response to treatment was assessed according to ACR20, ACR50, ACR70, and ACR90.

Endpoint: ACR20

		Treatment in core trial	
Visit	Total N=115	ACZ885 N=89	non-ACZ885 N=26
BAS	56/115 (48.7%)	42/89 (47.2%)	14/26 (53.8%)
DAY1	57/115 (49.6%)	41/89 (46.1%)	16/26 (61.5%)
WEEK6	62/108 (57.4%)	46/82 (56.1%)	16/26 (61.5%)
WEEK12	57/107 (53.3%)	39/82 (47.6%)	18/25 (72.0%)
WEEK18	61/104 (58.7%)	41/78 (52.6%)	20/26 (76.9%)
WEEK24	52/96 (54.2%)	37/71 (52.1%)	15/25 (60.0%)
WEEK30	51/83 (61.4%)	36/63 (57.1%)	15/20 (75.0%)
WEEK36	39/74 (52.7%)	30/57 (52.6%)	9/17 (52.9%)
WEEK42	28/49 (57.1%)	21/38 (55.3%)	7/11 (63.6%)
WEEK48	24/45 (53.3%)	18/36 (50.0%)	6/9 (66.7%)
FOLLOW-UP	20/48 (41.7%)	14/39 (35.9%)	6/9 (66.7%)
EOS	51/111 (45.9%)	35/86 (40.7%)	16/25 (64.0%)

Endpoint: ACR50

		Treatment in core trial	
Visit	Total N=115	ACZ885 N=89	non-ACZ885 N=26
BAS	27/115 (23.5%)	19/89 (21.3%)	8/26 (30.8%)
DAY1	27/115 (23.5%)	19/89 (21.3%)	8/26 (30.8%)
WEEK6	27/108 (25.0%)	18/82 (22.0%)	9/26 (34.6%)
WEEK12	33/107 (30.8%)	22/82 (26.8%)	11/25 (44.0%)
WEEK18	27/104 (26.0%)	19/78 (24.4%)	8/26 (30.8%)
WEEK24	31/96 (32.3%)	21/71 (29.6%)	10/25 (40.0%)
WEEK30	27/83 (32.5%)	18/63 (28.6%)	9/20 (45.0%)
WEEK36	26/74 (35.1%)	18/57 (31.6%)	8/17 (47.1%)
WEEK42	19/49 (38.8%)	13/38 (34.2%)	6/11 (54.5%)
WEEK48	13/45 (28.9%)	9/36 (25.0%)	4/9 (44.4%)
FOLLOW-UP	12/48 (25.0%)	8/39 (20.5%)	4/9 (44.4%)
EOS	29/111 (26.1%)	22/86 (25.6%)	7/25 (28.0%)

Endpoint: ACR70

Visit	Total N=115	Treatment in core trial: ACZ885 N=89	Treatment in core trial: non-ACZ885 N=26
BAS	14/115 (12.2%)	9/89 (10.1%)	5/26 (19.2%)
DAY1	13/115 (11.3%)	9/89 (10.1%)	4/26 (15.4%)
WEEK6	14/108 (13.0%)	10/82 (12.2%)	4/26 (15.4%)
WEEK12	14/107 (13.1%)	10/82 (12.2%)	4/25 (16.0%)
WEEK18	15/104 (14.4%)	11/78 (14.1%)	4/26 (15.4%)
WEEK24	16/96 (16.7%)	11/71 (15.5%)	5/25 (20.0%)
WEEK30	15/83 (18.1%)	9/63 (14.3%)	6/20 (30.0%)
WEEK36	15/74 (20.3%)	8/57 (14.0%)	7/17 (41.2%)
WEEK42	13/49 (26.5%)	9/38 (23.7%)	4/11 (36.4%)
WEEK48	6/45 (13.3%)	4/36 (11.1%)	2/9 (22.2%)
FOLLOW-UP	7/48 (14.6%)	4/39 (10.3%)	3/9 (33.3%)
EOS	17/111 (15.3%)	12/86 (14.0%)	5/25 (20.0%)

Endpoint: ACR90

Visit	Total N=115	Treatment in core trial: ACZ885 N=89	Treatment in core trial: non-ACZ885 N=26
BAS	3/115 (2.6%)	3/89 (3.4%)	0/26 (0.0%)
DAY1	3/115 (2.6%)	3/89 (3.4%)	0/26 (0.0%)
WEEK6	3/108 (2.8%)	2/82 (2.4%)	1/26 (3.8%)
WEEK12	3/107 (2.8%)	2/82 (2.4%)	1/25 (4.0%)
WEEK18	2/104 (1.9%)	2/78 (2.6%)	0/26 (0.0%)
WEEK24	5/96 (5.2%)	3/71 (4.2%)	2/25 (8.0%)
WEEK30	3/83 (3.6%)	2/63 (3.2%)	1/20 (5.0%)
WEEK36	5/74 (6.8%)	4/57 (7.0%)	1/17 (5.9%)
WEEK42	4/49 (8.2%)	3/38 (7.9%)	1/11 (9.1%)
WEEK48	3/45 (6.7%)	2/36 (5.6%)	1/9 (11.1%)
FOLLOW-UP	5/48 (10.4%)	4/39 (10.3%)	1/9 (11.1%)
EOS	6/111 (5.4%)	5/86 (5.8%)	1/25 (4.0%)

Summary of subjects in clinical remission by time (Safety analysis set)

Visit	Total N=115	Treatment in core trial: ACZ885 N=89	Treatment in core trial: non-ACZ885 N=26
BAS	13/115 (11.3%)	9/89 (10.1%)	4/26 (15.4%)
DAY1	17/115 (14.8%)	12/89 (13.5%)	5/26 (19.2%)
WEEK6	18/108 (16.7%)	14/82 (17.1%)	4/26 (15.4%)
WEEK12	20/107 (18.7%)	16/82 (19.5%)	4/25 (16.0%)
WEEK18	20/104 (19.2%)	14/78 (17.9%)	6/26 (23.1%)
WEEK24	20/96 (20.8%)	14/71 (19.7%)	6/25 (24.0%)
WEEK30	20/83 (24.1%)	14/63 (22.2%)	6/20 (30.0%)
WEEK36	14/74 (18.9%)	9/57 (15.8%)	5/17 (29.4%)
WEEK42	16/49 (32.7%)	11/38 (28.9%)	5/11 (45.5%)
WEEK48	8/45 (17.8%)	6/36 (16.7%)	2/9 (22.2%)
FOLLOW-UP	13/47 (27.7%)	9/38 (23.7%)	4/9 (44.4%)
EOS	20/110 (18.2%)	14/85 (16.5%)	6/25 (24.0%)

Clinical response to treatment was assessed by ACR components that are Tender 28-joint count and swollen 28-joint count, Patient's assessment of pain intensity, Global assessment of disease activity, and acute phase reactant CRP.

Summary of 28-joint count (total swollen and tender count) by time. Safety analysis set

		Swollen joints (right & left)			Tender joints (right & left)		
			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
COREBAS	n	115	89	26	115	89	26
	mean	11.8	11.9	11.6	16.4	16.2	17.1
	SD	4.80	4.74	5.10	6.57	6.32	7.47
	minimum	1	1	4	4	4	4
	median	11.0	11.0	10.0	15.0	15.0	18.3
	maximum	25	25	20	28	28	28
BAS	n	115	89	26	115	89	26
	mean	6.0	5.8	6.3	9.3	9.4	8.9
	SD	5.10	5.13	5.07	7.70	7.64	8.04
	minimum	0	0	0	0	0	0
	median	5.0	4.0	5.0	7.0	7.0	7.0
	maximum	22	22	15	28	28	24
DAY1	n	114	88	26	114	88	26
	mean	6.5	6.6	6.1	9.5	9.7	9.1
	SD	5.53	5.77	4.69	8.11	8.26	7.70
	minimum	0	0	0	0	0	0
	median	5.0	5.0	6.0	7.0	7.0	8.1
	maximum	23	23	15	28	28	27
WEEK6	n	108	82	26	108	82	26
	mean	5.8	6.1	4.7	8.7	8.8	8.1
	SD	5.65	6.03	4.18	7.70	7.68	7.88
	minimum	0	0	0	0	0	0
	median	4.0	4.0	3.1	6.0	6.5	5.0
	maximum	24	24	14	28	28	27

Visit		Swollen joints (right & left) Total N=115	Swollen joints (right & left) Treatment in core trial ACZ885 N=89	Swollen joints (right & left) Treatment in core trial non-ACZ885 N=26	Tender joints (right & left) Total N=115	Tender joints (right & left) Treatment in core trial ACZ885 N=89	Tender joints (right & left) Treatment in core trial non-ACZ885 N=26
WEEK12	n	106	81	25	106	81	25
	mean	5.2	5.6	3.9	7.9	8.2	7.0
	SD	5.16	5.38	4.17	7.17	7.22	7.06
	minimum	0	0	0	0	0	0
	median	3.5	4.0	3.0	6.0	6.0	5.0
	maximum	22	22	17	26	26	21
WEEK18	n	101	75	26	101	75	26
	mean	5.0	4.9	5.5	7.7	7.6	8.0
	SD	5.18	5.15	5.34	7.15	6.80	8.20
	minimum	0	0	0	0	0	0
	median	3.0	4.0	3.0	6.0	5.0	6.0
	maximum	24	24	18	27	27	26
WEEK24	n	89	65	24	89	65	24
	mean	4.4	4.3	4.6	7.1	6.9	7.7
	SD	4.35	4.36	4.43	7.40	7.53	7.16
	minimum	0	0	0	0	0	0
	median	3.0	3.0	5.0	4.0	3.0	7.0
	maximum	18	16	18	28	28	20
WEEK30	n	75	56	19	75	56	19
	mean	3.9	3.9	3.8	6.9	6.9	7.0
	SD	4.37	4.38	4.45	7.54	7.51	7.81
	minimum	0	0	0	0	0	0
	median	3.0	2.5	3.0	4.0	4.0	2.0
	maximum	22	22	17	25	25	25

Visit		Swollen joints (right & left) Total N=115	Swollen joints (right & left) Treatment in core trial ACZ885 N=89	Swollen joints (right & left) Treatment in core trial non-ACZ885 N=26	Tender joints (right & left) Total N=115	Tender joints (right & left) Treatment in core trial ACZ885 N=89	Tender joints (right & left) Treatment in core trial non-ACZ885 N=26
WEEK36	n	64	48	16	64	48	16
	mean	3.5	3.5	3.6	6.9	6.8	7.3
	SD	4.65	4.33	5.68	7.19	6.76	8.60
	minimum	0	0	0	0	0	0
	median	2.0	2.0	1.5	4.0	4.0	4.0
	maximum	20	18	20	25	23	25
WEEK42	n	38	29	9	38	29	9
	mean	3.8	4.1	2.9	3.8	4.3	2.2
	SD	4.60	4.93	3.41	6.12	6.68	3.67
	minimum	0	0	0	0	0	0
	median	2.0	2.0	2.0	1.0	1.0	1.0
	maximum	20	20	11	26	26	10
WEEK48	n	34	27	7	34	27	7
	mean	4.4	4.3	4.4	4.9	5.4	2.6
	SD	4.99	5.13	4.79	6.33	6.90	2.51
	minimum	0	0	0	0	0	0
	median	3.0	3.0	2.0	3.6	4.0	3.0
	maximum	19	19	11	28	28	7
FOLLOW-UP	n	35	28	7	35	28	7
	mean	3.9	4.4	1.9	5.9	6.7	2.7
	SD	5.22	5.61	2.54	7.11	7.61	3.35
	minimum	0	0	0	0	0	0
	median	2.0	2.5	1.0	4.0	4.5	1.0
	maximum	23	23	6	27	27	8

Visit		Swollen joints (right & left) Total N=115	Swollen joints (right & left) Treatment in core trial ACZ885 N=89	Swollen joints (right & left) Treatment in core trial non-ACZ885 N=26	Tender joints (right & left) Total N=115	Tender joints (right & left) Treatment in core trial ACZ885 N=89	Tender joints (right & left) Treatment in core trial non-ACZ885 N=26
EOS	n	109	84	25	109	84	25
	mean	5.1	5.0	5.2	7.6	7.8	6.9
	SD	5.18	5.43	4.32	7.25	7.46	6.60
	minimum	0	0	0	0	0	0
	median	3.0	3.0	3.0	5.0	5.5	4.1
	maximum	20	20	13	26	26	19

Summary of patient's assessment of pain intensity (100mm VAS) by time (Safety analysis set)

		Pain over the last 24h VAS (mm)		
			Treatment in core trial	
		Total	ACZ885	non-ACZ885
Visit		N=115	N=89	N=26
COREBAS	n	115	89	26
	mean	60.3	60.2	60.7
	SD	18.34	18.19	19.20
	minimum	9	9	19
	median	60.0	61.0	58.5
	maximum	100	100	99
BAS	n	114	89	25
	mean	42.3	43.6	37.9
	SD	21.93	21.98	21.59
	minimum	0	0	1
	median	43.0	45.0	35.0
	maximum	93	93	75
DAY1	n	114	88	26
	mean	41.2	42.4	36.9
	SD	21.60	21.29	22.51
	minimum	0	0	3
	median	42.5	44.5	33.5
	maximum	94	94	82
WEEK6	n	108	82	26
	mean	37.8	39.4	32.5
	SD	21.16	21.10	20.88
	minimum	0	0	2
	median	37.0	42.0	29.0
	maximum	95	95	78

		Pain over the last 24h VAS (mm)		
			Treatment in core trial	
		Total	ACZ885	non-ACZ885
Visit		N=115	N=89	N=26
WEEK12	n	106	81	25
	mean	37.1	38.5	32.7
	SD	21.21	20.89	22.06
	minimum	0	0	2
	median	36.0	39.0	29.0
	maximum	83	83	73
WEEK18	n	101	75	26
	mean	39.4	40.4	36.6
	SD	21.35	20.79	23.09
	minimum	0	1	0
	median	38.0	40.0	30.5
	maximum	88	77	88
WEEK24	n	88	64	24
	mean	36.8	37.6	34.5
	SD	20.55	20.64	20.60
	minimum	0	0	2
	median	38.0	38.5	37.5
	maximum	75	75	74
WEEK30	n	74	55	19
	mean	36.3	37.3	33.4
	SD	21.13	21.11	21.50
	minimum	0	0	0
	median	35.0	37.0	30.0
	maximum	79	79	77

		Pain over the last 24h VAS (mm)		
			Treatment in core trial	
		Total	ACZ885	non-ACZ885
Visit		N=115	N=89	N=26
WEEK36	n	64	48	16
	mean	36.5	37.3	34.3
	SD	23.01	22.68	24.60
	minimum	0	0	3
	median	33.5	37.5	25.5
	maximum	80	74	80
WEEK42	n	37	28	9
	mean	32.5	35.0	24.4
	SD	21.11	22.43	14.54
	minimum	0	0	4
	median	27.0	33.0	26.0
	maximum	77	77	52
WEEK48	n	34	27	7
	mean	33.0	34.8	25.9
	SD	21.24	22.17	16.61
	minimum	0	0	4
	median	29.5	35.0	21.0
	maximum	83	83	50
FOLLOW-UP	n	33	26	7
	mean	35.9	38.8	25.4
	SD	22.12	23.09	14.99
	minimum	0	0	3
	median	32.0	33.5	22.0
	maximum	84	84	45

Visit		Pain over the last 24h VAS (mm) Total N=115	Treatment in core trial ACZ885 N=89	non-ACZ885 N=26
EOS	n	108	83	25
	mean	40.1	41.7	34.9
	SD	20.60	20.28	21.25
	minimum	0	0	0
	median	41.0	44.0	26.0
	maximum	82	82	82

Summary of global assessment of disease activity (100mm VAS) by time (Safety analysis set)

		Assessment VAS (mm)					
		Patient			Investigator		
		Treatment in core trial			Treatment in core trial		
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
COREBAS	n	114	88	26	114	88	26
	mean	64.5	64.1	65.9	62.3	60.9	67.1
	SD	17.71	18.41	15.34	15.67	13.72	20.59
	minimum	8	8	39	18	24	18
	median	65.0	65.0	62.5	63.0	62.0	72.0
	maximum	100	100	95	92	90	92
BAS	n	114	89	25	114	89	25
	mean	45.0	46.4	39.9	37.0	36.9	37.3
	SD	23.05	22.19	25.70	23.11	23.30	22.90
	minimum	0	0	4	0	0	5
	median	46.5	48.0	32.0	33.5	34.0	31.0
	maximum	96	96	77	90	90	85
DAY1	n	114	88	26	115	89	26
	mean	44.1	45.4	39.6	38.7	39.1	37.2
	SD	21.96	21.67	22.77	23.09	23.22	23.03
	minimum	0	0	3	0	0	1
	median	46.5	48.0	36.5	36.0	37.0	34.5
	maximum	96	96	77	90	90	72
WEEK6	n	108	82	26	108	82	26
	mean	40.3	42.8	32.4	34.1	36.8	25.9
	SD	22.02	21.95	20.69	22.70	24.23	14.46
	minimum	1	1	1	1	1	1
	median	39.5	48.0	29.5	29.0	31.5	26.0
	maximum	95	95	76	90	90	60

		Assessment VAS (mm)					
		Patient			Investigator		
			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
WEEK12	n	106	81	25	106	81	25
	mean	39.9	42.1	32.9	33.0	35.1	26.4
	SD	21.01	20.85	20.37	21.82	21.97	20.38
	minimum	0	0	2	2	2	2
	median	40.5	46.0	29.0	32.5	36.0	17.0
	maximum	83	83	76	84	84	62
WEEK18	n	101	75	26	101	75	26
	mean	42.0	44.3	35.3	33.7	33.1	35.6
	SD	20.89	20.80	20.07	22.06	21.27	24.57
	minimum	0	0	8	0	0	0
	median	42.0	46.0	30.0	31.0	29.0	34.5
	maximum	83	83	81	85	83	85
WEEK24	n	88	64	24	88	64	24
	mean	38.3	40.2	33.0	27.8	28.8	25.0
	SD	21.04	20.99	20.69	20.25	20.14	20.70
	minimum	0	0	2	0	0	1
	median	38.5	43.0	28.5	25.0	26.0	22.0
	maximum	80	80	69	92	92	79
WEEK30	n	75	56	19	75	56	19
	mean	36.6	38.0	32.5	26.0	26.7	24.0
	SD	21.97	22.46	20.48	16.79	16.32	18.42
	minimum	0	0	3	0	0	3
	median	31.0	33.5	31.0	24.0	25.0	17.0
	maximum	89	89	69	74	74	64

		Assessment VAS (mm)					
		Patient			Investigator		
			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
WEEK36	n	64	48	16	64	48	16
	mean	39.9	41.3	35.8	24.6	25.1	23.1
	SD	21.70	20.80	24.46	16.35	15.70	18.65
	minimum	0	0	4	0	0	3
	median	41.0	42.0	31.0	22.0	22.5	19.0
	maximum	83	83	78	73	72	73
WEEK42	n	37	28	9	37	28	9
	mean	31.2	33.6	23.9	21.3	20.0	25.3
	SD	21.40	23.40	11.57	17.25	16.53	19.81
	minimum	0	0	5	0	0	2
	median	29.0	30.5	26.0	16.0	14.5	19.0
	maximum	82	82	36	64	64	63
WEEK48	n	34	27	7	34	27	7
	mean	37.6	40.0	28.1	23.3	24.0	20.9
	SD	23.08	24.48	14.24	18.10	18.59	17.17
	minimum	0	0	4	0	0	0
	median	36.5	43.0	30.0	22.0	22.0	23.0
	maximum	87	87	46	69	69	48
FOLLOW-UP	n	33	26	7	33	26	7
	mean	38.4	43.6	19.1	27.6	31.0	14.7
	SD	23.99	23.67	13.61	23.70	24.51	15.70
	minimum	0	0	3	1	1	2
	median	39.0	46.0	16.0	19.0	25.0	9.0
	maximum	94	94	39	87	87	48

		Assessment VAS (mm)					
		Patient			Investigator		
			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
EOS	n	109	84	25	108	84	24
	mean	42.0	42.7	39.8	32.7	32.9	31.9
	SD	21.77	21.34	23.45	22.88	22.18	25.69
	minimum	0	0	0	0	0	0
	median	45.0	47.5	38.0	28.5	30.0	25.5
	maximum	89	89	89	97	95	97

Summary of acute phase reactant CRP by time (Safety analysis set)

Total (N=115)

			Statistics							
Parameter	Unit	Visit	n	mean	SD	minimum	median	maximum	CV	n(log)	geometric mean
PROTCHS	mg/L	COREBAS	111	25.18	30.345	0.2	11.90	173.4	120.5	111	12.78
		BAS	99	14.42	22.406	0.1	5.40	104.8	155.4	99	5.56
		DAY1	114	15.30	26.827	0.1	5.10	153.6	175.3	114	4.99
		WEEK6	108	10.38	16.717	0.2	3.45	81.2	161.1	108	3.89
		WEEK12	105	10.10	19.355	0.1	2.80	135.2	191.7	105	3.45
		WEEK18	101	9.99	16.948	0.1	2.60	96.8	169.7	101	3.61
		WEEK24	89	8.35	16.413	0.2	2.40	93.8	196.5	89	2.85
		WEEK30	75	8.03	14.065	0.1	2.90	81.9	175.2	75	3.19
		WEEK36	62	6.49	10.146	0.3	2.45	55.6	156.4	62	2.80
		WEEK42	35	5.71	10.577	0.4	2.70	59.9	185.4	35	2.57
		WEEK48	33	6.72	11.545	0.4	2.80	52.6	171.7	33	2.87
		FOLLOW-UP	35	6.71	12.611	0.2	2.70	60.1	187.9	35	2.42
		EOS	106	10.74	22.520	0.2	2.95	190.0	209.7	106	3.73

Summary of change from baseline in total RAMRIS scores (MRI) Safety analysis set

Subjects from core trial CACZ885A2204

Core treatment	Visit	Edema score n	Edema score median	Edema score (min-max)	Erosion score n	Erosion score median	Erosion score (min-max)	Synovitis score n	Synovitis score median	Synovitis score (min-max)
ACZ885	WEEK18	26	0	(-0.39-0.04)	32	0	(-0.13-0.09)	27	-0.143	(-1.86-0.57)
non-ACZ885	WEEK18	14	-0.043	(-0.86-3.00)	15	0	(-0.39-0.30)	11	-0.714	(-1.43-0.14)

Summary of BMD (DXA) by site (Safety analysis set)

Subjects from core trial CACZ885A2204
ACZ885 treatment in core trial: Yes

BMD evaluation location	BMD region	Visit	Statistics n	mean	SD	minimum	median	maximum
AP lumbar spine	L1	COREBAS	8	1.0509	0.22463	0.755	1.0265	1.542
		WEEK18	4	1.1043	0.30027	0.800	1.0510	1.515
	L2	COREBAS	8	1.0909	0.23216	0.712	1.0665	1.555
		WEEK18	4	1.1305	0.35297	0.792	1.0515	1.627
	L3	COREBAS	8	1.1278	0.27894	0.767	1.0990	1.725
		WEEK18	4	1.2455	0.40567	0.785	1.2115	1.774
	L4	COREBAS	8	1.1046	0.27494	0.745	1.0640	1.700
		WEEK18	4	1.1653	0.38414	0.793	1.0820	1.704
	L1-L4	COREBAS	8	1.0951	0.25329	0.746	1.0695	1.639
		WEEK18	4	1.1650	0.36399	0.792	1.1015	1.665
Hip	Total hip	COREBAS	8	0.9391	0.24343	0.564	0.8965	1.398
		WEEK18	4	0.9000	0.32558	0.571	0.8400	1.349
	Femoral neck	COREBAS	8	0.8959	0.25665	0.593	0.8455	1.378
		WEEK18	4	0.8728	0.32003	0.572	0.7990	1.321
	Wards triangle	COREBAS	8	0.7309	0.27755	0.426	0.6905	1.314
		WEEK18	4	0.7193	0.33969	0.397	0.6460	1.188
	Trochanter	COREBAS	8	0.7554	0.22145	0.374	0.7955	1.123
		WEEK18	4	0.6968	0.27449	0.426	0.6430	1.075

Subjects from core trial CACZ885A2204
ACZ885 treatment in core trial: Yes

BMD evaluation location	BMD region	Visit	Statistics n	mean	SD	minimum	median	maximum
Hip	Femoral shaft	COREBAS	8	1.1174	0.29348	0.699	1.0635	1.655
		WEEK18	4	1.0675	0.39133	0.687	0.9855	1.612
Hand	Total hand	COREBAS	8	0.4340	0.12922	0.194	0.4700	0.584
		WEEK18	4	0.3295	0.09726	0.207	0.3330	0.445

Subjects from core trial CACZ885A2204
ACZ885 treatment in core trial: No

BMD evaluation location	BMD region	Visit	Statistics n	mean	SD	minimum	median	maximum
AP lumbar spine	L1	COREBAS	2	1.0915	0.07990	1.035	1.0915	1.148
		WEEK18	1	1.1490		1.149	1.1490	1.149
	L2	COREBAS	2	1.1735	0.11102	1.095	1.1735	1.252
		WEEK18	1	1.1340		1.134	1.1340	1.134
	L3	COREBAS	2	1.2135	0.05162	1.177	1.2135	1.250
		WEEK18	1	1.2230		1.223	1.2230	1.223
	L4	COREBAS	2	1.1305	0.06152	1.087	1.1305	1.174
		WEEK18	1	1.1870		1.187	1.1870	1.187
	L1-L4	COREBAS	2	1.1530	0.07354	1.101	1.1530	1.205
		WEEK18	1	1.1760		1.176	1.1760	1.176
Hip	Total hip	COREBAS	2	0.9875	0.11526	0.906	0.9875	1.069
		WEEK18	1	0.8570		0.857	0.8570	0.857
	Femoral neck	COREBAS	2	1.0570	0.11031	0.979	1.0570	1.135
		WEEK18	1	0.8740		0.874	0.8740	0.874
	Wards triangle	COREBAS	2	0.8370	0.20365	0.693	0.8370	0.981
		WEEK18	1	0.6330		0.633	0.6330	0.633
	Trochanter	COREBAS	2	0.7450	0.13435	0.650	0.7450	0.840
		WEEK18	1	0.5810		0.581	0.5810	0.581

Subjects from core trial CACZ885A2204
ACZ885 treatment in core trial: No

BMD evaluation location	BMD region	Visit	Statistics n	mean	SD	minimum	median	maximum
Hip	Femoral shaft	COREBAS	2	1.1885	0.09546	1.121	1.1885	1.256
		WEEK18	1	1.0750		1.075	1.0750	1.075
Hand	Total hand	COREBAS	2	0.4405	0.05020	0.405	0.4405	0.476
		WEEK18	1	0.4280		0.428	0.4280	0.428

Summary of change from baseline in total Sharp / van der Heijde scores (X-ray, Safety analysis set)

Subjects from core trial CACZ885A2204

X-ray site	Core treatment	Visit	Erosion score n	Erosion score median	Erosion score (min-max)	Joint narrowing score n	Joint narrowing score median	Joint narrowing score (min-max)
Left hand	ACZ885	WEEK18	33	0	(-0.06-0.13)	33	0	(0.00-0.13)
	non-ACZ885	WEEK18	16	0	(0.00-0.63)	16	0	(-0.07-0.07)
Right hand	ACZ885	WEEK18	33	0	(0.00-0.25)	33	0	(-0.07-0.07)
	non-ACZ885	WEEK18	16	0	(0.00-0.38)	16	0	(-0.07-0.07)
Left foot	ACZ885	WEEK18	33	0	(-0.17-1.00)	33	0	(0.00-0.50)
	non-ACZ885	WEEK18	16	0	(0.00-0.50)	16	0	(0.00-0.00)
Right foot	ACZ885	WEEK18	33	0	(0.00-1.00)	33	0	(0.00-0.17)
	non-ACZ885	WEEK18	16	0	(0.00-0.67)	16	0	(0.00-0.00)

Summary of immunogenicity (Safety analysis set)

Visit	Immunogenicity	Total N=115 n (%)
COREBAS	NO	108 (93.91%)
	BLQ	0
	ALQ	1 (0.87%)
DAY1	NO	94 (81.74%)
	BLQ	0
	ALQ	0
WEEK6	NO	1 (0.87%)
	BLQ	0
	ALQ	0
WEEK12	NO	89 (77.39%)
	BLQ	0
	ALQ	0
WEEK24	NO	73 (63.48%)
	BLQ	0
	ALQ	0
WEEK36	NO	46 (40%)
	BLQ	0
	ALQ	0
WEEK48	NO	21 (18.26%)
	BLQ	0
	ALQ	0
EOS	NO	93 (80.87%)
	BLQ	0
	ALQ	0

Immunogenicity: NO (no immunogenicity), BLQ (positive immunogenicity < LLOQ (not quantifiable)), ALQ (positive immunogenicity > LLOQ (quantifiable)

Long-term (PK) assessed (PK Analysis Set):

The PK parameters of canakinumab were in line with the expected PK characteristics of a human IgG molecule. In brief, for the study population, the mean serum clearance (CL) of canakinumab was 0.210 L/d with a low mean total volume of distribution (Vss = VD+VP) of 6.13 L.

Summary of Individual pharmacokinetic and binding parameters in adult (18 years or older) RA patients (n=115)

Table	CLD [L/d]	VD [L]	VP [L]
Mean	0.210	3.34	2.79
SD	0.0741	1.03	0.772
Median	0.201	3.12	2.76
Min	0.0851	1.38	0.835
Max	0.508	9.27	6.53
CV%	35.3	30.7	27.6

CL ([apparent] clearance), Vd ([apparent] volume of distribution), Vp (volume of distribution of the tissue fluid compartment)

Summary of HAQ and SF-36 Summary Scores by Time-Safety Analysis Set

		HAQ score			SF-36 summary scores					
					Physical component			Mental component		
			Treatment in core trial			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
COREBAS	n	115	89	26	108	83	25	108	83	25
	mean	1.534	1.577	1.388	31.432	31.221	32.136	41.770	42.181	40.407
	SD	0.6722	0.6539	0.7257	7.4968	7.6852	6.9353	11.6349	12.2542	9.3781
	minimum	0.00	0.00	0.00	14.02	14.02	19.73	16.03	16.03	22.34
	median	1.625	1.625	1.500	31.192	30.393	33.030	41.543	42.173	40.750
	maximum	2.88	2.88	2.71	46.11	46.11	45.89	64.64	64.64	59.51
BAS	n	109	83	26	101	78	23	101	78	23
	mean	1.107	1.169	0.909	38.115	37.549	40.036	44.947	44.382	46.864
	SD	0.6957	0.6853	0.7049	9.9799	10.0865	9.5729	11.9800	12.3125	10.8074
	minimum	0.00	0.00	0.00	16.78	18.78	16.78	21.56	21.56	24.71
	median	1.125	1.125	1.000	36.501	36.205	39.819	43.498	42.285	48.797
	maximum	2.75	2.75	2.38	61.51	61.51	58.78	70.84	70.84	62.09
DAY1	n	112	87	25	0	0	0	0	0	0
	mean	1.039	1.101	0.825						
	SD	0.7271	0.7276	0.6978						
	minimum	0.00	0.00	0.00						
	median	1.000	1.000	0.875						
	maximum	2.88	2.88	2.38						
WEEK6	n	106	82	24	0	0	0	0	0	0
	mean	0.981	1.052	0.740						
	SD	0.6990	0.6980	0.6603						
	minimum	0.00	0.00	0.00						
	median	0.875	1.000	0.563						
	maximum	2.75	2.75	2.50						

		HAQ score			SF-36 summary scores					
					Physical component			Mental component		
			Treatment in core trial			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
WEEK12	n	103	78	25	91	72	19	91	72	19
	mean	1.044	1.095	0.885	39.374	38.625	42.211	45.867	45.937	45.600
	SD	0.6924	0.7017	0.6504	9.7656	9.7443	9.5685	12.5364	12.9690	11.0574
	minimum	0.00	0.00	0.00	17.11	17.11	26.82	19.47	19.47	24.06
	median	1.000	1.063	0.750	38.917	38.587	43.247	48.461	48.345	50.249
	maximum	2.75	2.75	2.38	59.42	59.42	57.38	67.77	67.77	61.80
WEEK18	n	98	74	24	0	0	0	0	0	0
	mean	1.061	1.147	0.797						
	SD	0.7182	0.7063	0.7040						
	minimum	0.00	0.00	0.00						
	median	1.000	1.125	0.625						
	maximum	2.75	2.75	2.38						
WEEK24	n	88	64	24	81	58	23	81	58	23
	mean	0.997	1.027	0.917	39.437	38.913	40.758	44.701	44.307	45.694
	SD	0.7224	0.7076	0.7703	9.2349	8.7241	10.5061	11.9993	12.1984	11.6877
	minimum	0.00	0.00	0.00	20.26	20.26	26.05	17.96	17.96	20.16
	median	1.000	1.000	0.688	38.605	38.187	39.343	45.119	43.877	45.528
	maximum	2.63	2.63	2.25	61.35	57.75	61.35	64.60	63.91	64.60
WEEK30	n	73	54	19	0	0	0	0	0	0
	mean	0.993	1.074	0.763						
	SD	0.7223	0.7152	0.7107						
	minimum	0.00	0.00	0.00						
	median	1.000	1.125	0.500						
	maximum	2.63	2.63	2.13						

		HAQ score			SF-36 summary scores					
					Physical component			Mental component		
			Treatment in core trial			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
WEEK36	n	64	48	16	55	42	13	55	42	13
	mean	1.008	1.055	0.867	38.264	37.387	41.095	45.175	46.739	40.122
	SD	0.7450	0.7451	0.7507	10.0517	9.1484	12.5436	12.1436	11.8686	12.0873
	minimum	0.00	0.00	0.00	21.15	21.15	27.25	17.53	17.53	19.28
	median	1.063	1.063	0.875	35.989	35.951	40.905	47.495	48.431	34.478
	maximum	2.88	2.88	2.25	63.30	58.99	63.30	65.74	65.74	59.13
WEEK42	n	37	28	9	0	0	0	0	0	0
	mean	0.814	0.920	0.486						
	SD	0.8368	0.9231	0.3391						
	minimum	0.00	0.00	0.00						
	median	0.625	0.750	0.375						
	maximum	2.88	2.88	0.88						
WEEK48	n	33	27	6	30	24	6	30	24	6
	mean	0.837	0.917	0.479	40.110	39.813	41.296	49.993	49.353	52.551
	SD	0.7529	0.7890	0.4501	10.3660	9.8624	13.1794	13.0069	13.6066	10.9446
	minimum	0.00	0.00	0.00	24.23	24.23	28.20	18.57	18.57	34.05
	median	0.750	0.875	0.313	39.849	39.849	38.849	52.059	52.059	53.983
	maximum	2.50	2.50	1.25	61.64	60.12	61.64	71.21	71.21	63.13
FOLLOW-UP	n	32	25	7	0	0	0	0	0	0
	mean	0.859	0.960	0.500						
	SD	0.7231	0.7601	0.4449						
	minimum	0.00	0.00	0.00						
	median	0.875	1.000	0.375						
	maximum	2.75	2.75	1.25						

					SF-36 summary scores					
		HAQ score			Physical component			Mental component		
			Treatment in core trial			Treatment in core trial			Treatment in core trial	
Visit		Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26	Total N=115	ACZ885 N=89	non-ACZ885 N=26
EOS	n	109	84	25	103	79	24	103	79	24
	mean	1.089	1.149	0.890	38.295	37.203	41.889	42.346	41.921	43.746
	SD	0.7350	0.7251	0.7477	9.4491	8.7430	10.9160	11.8792	11.6246	12.8402
	minimum	0.00	0.00	0.00	20.22	20.22	23.90	16.47	16.47	19.40
	median	1.000	1.125	0.750	36.474	36.208	41.383	41.087	41.492	40.923
	maximum	2.88	2.88	2.50	62.14	59.49	62.14	65.89	62.21	65.89

Safety Results

Adverse Events by System Organ Class

Table 12-2 Incidence of AEs by primary system organ class (Safety set)

	Total N=115 n	(%)
Patients with AE(s)	91	(79%)
System organ class		
Infections and infestations	50	(43%)
Musculoskeletal and connective tissue disorders	31	(27%)
Gastrointestinal disorders	23	(20%)
Investigations	18	(16%)
Nervous system disorders	18	(16%)
Skin and subcutaneous tissue disorders	15	(13%)
Injury, poisoning and procedural complications	13	(11%)
General disorders and administration site conditions	10	(9%)
Respiratory, thoracic and mediastinal disorders	9	(8%)
Blood and lymphatic system disorders	6	(5%)
Renal and urinary disorders	6	(5%)
Cardiac disorders	5	(4%)
Eye disorders	5	(4%)
Metabolism and nutrition disorders	5	(4%)
Vascular disorders	5	(4%)
Ear and labyrinth disorders	3	(3%)
Hepatobiliary disorders	3	(3%)
Immune system disorders	3	(3%)
Psychiatric disorders	3	(3%)
Reproductive system and breast disorders	3	(3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	(2%)
Congenital, familial and genetic disorders	1	(1%)
Endocrine disorders	1	(1%)
Social circumstances	1	(1%)
Surgical and medical procedures	1	(1%)

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

Patients with AE(s)	91	(79%)
Nasopharyngitis	12	(10%)
Headache	11	(10%)
Bronchitis	8	(7%)
Pain in extremity	7	(6%)
Respiratory tract infection viral	7	(6%)
Back pain	6	(5%)
Rheumatoid arthritis	6	(5%)
Arthralgia	5	(4%)
Nausea	5	(4%)
Abdominal pain upper	4	(3%)

Serious Adverse Events and Deaths

No. (%) of subjects studied	115
No. (%) of subjects with AE(s)	91 (79%)
Number (%) of subjects with serious or other significant events	n (%)
Death	1 (1%)
SAE(s)	8 (7%)
Discontinued due to SAE(s)	3 (3%)

SAEs: 1 hip fracture (leading to death), 1 osteoarthritis, 1 radius fracture, 1 intermediate uveitis and sarcoidosis, 1 back pain and spinal fracture, 1RA, 1 colon neoplasm, 1 cholelithiasis, 1 lower respiratory tract infection.

Other Relevant Findings

The population-based PK-binding model captures the kinetics of canakinumab as well as the in- crease in the total IL-1β concentrations. The PK parameters of canakinumab estimated from the binding model were very similar to a human IgG1-type antibody. The mean total distribution volume (VD+VP) in adult patients was approximately 6.13 L, which is close to the serum volume and typical for the distribution of large macromolecules. Mean total serum clearance (CL) was slow, estimated to be 0.210 L/day in adult patients. An increase in total IL-1β levels was observed following canakinumab dosing, signifying the binding of IL-1β to canakinumab. The mean equilibrium dissociation constant for binding of canakinumab to IL-1β was estimated to be 0.557 nM.

Conclusion:

The development of ACZ885 in the RA indication was terminated while this study was ongoing. The study was prematurely stopped by the sponsor and most of the patients were discontinued from the study before its completion. The study met its objectives only partially since a number of the planned analysis could not be performed. The AE profile for ACZ885 observed in this study does not indicate target organ toxicity. Additionally, good local tolerability at the injection site was documented. Overall ACZ885 was safe and well tolerated. This study also adds to the evidence suggesting a very low immunogenicity potential for ACZ885 in this RA population. From the efficacy side, no conclusion can be drawn from this extension study, as the dose and frequency of ACZ885 exposure was heterogeneous in the original studies 0 responders did not significantly change over time in the different groups.

Date of Clinical Study Report

01-Nov-2010

Date Inclusion on Novartis Clinical Trial Results Database

26-Nov-2010