Sponsor:

Novartis Pharmaceuticals

Generic Drug Name:

CFZ533

Trial Indication(s):

Rheumatoid Arthritis

Protocol Number:

CCFZ533X2101

Protocol Title:

A randomized, double-blind, placebo-controlled, single ascending dose first-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of CFZ533 in healthy subjects and rheumatoid arthritis patients

Clinical Trial Phase:

Phase I

Phase of Drug Development:

Phase II

Study Start/End Dates:

07 Jan 2013 to 03 Feb 2017

Reason for Termination (If applicable):

Study Design/Methodology:

First-in-Human, non-confirmatory, randomized, double-blind, placebo-controlled, single-ascending dose study. The study was conducted in 7 centers and utilized a 2 part design. Part 1 evaluated single ascending doses of CFZ533 (0.03, 0.1, 0.3, 1 and 3 mg/kg) and placebo administered as an IV infusion over approximately 1-2 hours in non-Chinese healthy subjects (Cohorts 1 through 5), healthy subjects of Chinese descent (3 mg/kg and placebo, Cohort 9) and patients with rheumatoid arthritis (10 and 30 mg/kg and placebo, Cohorts 6 and 7). Part 2 evaluated a single SC dose of 3 mg/kg CFZ533 and placebo in healthy subjects (Cohort 8).

Centers:

7 centers in 2 countries: USA (6), Taiwan (1)

Objectives:

The primary objective of the study was:

To evaluate the safety and tolerability of single, ascending doses of CFZ533 administered via intravenous (IV) infusion or subcutaneous (SC) injection in healthy adult subjects and via IV infusion in rheumatoid arthritis patients.

The secondary objectives of the study were:

To assess the pharmacokinetics (PK) of single doses of CFZ533 in healthy subjects and rheumatoid arthritis patients.

To evaluate the immunogenicity of single doses of CFZ533 via the quantitative analysis for anti-CFZ533 antibodies in healthy subjects and rheumatoid arthritis patients.

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

Single doses of CFZ533 were administered by IV infusion (0.03, 0.1, 0.3, 1, 3, 10 or 30 mg/kg) or SC injection (3 mg/kg).

Statistical Methods:

No formal statistical analyses were conducted and descriptive statistics were used to assess the endpoints throughout. In general, data from healthy subjects and patients with rheumatoid arthritis were summarized separately. Data from subjects treated with placebo were pooled across Cohorts 1 to 5 and 8 for non-Chinese healthy subjects and across Cohorts 6 and 7 for patients with rheumatoid arthritis. Data from Cohort 9 in Chinese healthy subjects were summarized separately, and compared to non-Chinese Cohort 5 for comparison.
Summary tables with the number, percentage, and severity of AEs were provided to assess safety and tolerability by treatment group. The number and percentage of subjects with AE were tabulated by body system and preferred term with a breakdown by treatment group.
All data for vital signs, ECG evaluations, clinical laboratory evaluations, PK, PD and biomarker parameters were listed for each subject and summarized by treatment group, and visit/time as appropriate. Boxplots to visualize trends in longitudinal safety data (biochemistry, hematology, vital signs and ECG) were also created. Graphical representations for PK, PD, biomarkers, rheumatoid arthritis markers and cytokines, were provided where appropriate.

Five interim analyses were conducted over the course of the study to aid decision making and dose escalation decisions and to aid dose selection for Proof-of-Concept studies.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria (for healthy subjects):

- Healthy male and surgically sterilized or post-menopausal female subjects 18 to 55 years of age (for Cohort 9 only, subjects had to be of Chinese descent)
- Vital signs (systolic and diastolic blood pressure and pulse rate) should have been within normal limits
- Weight 50-150 kg and a body mass index (BMI) 18-32 kg/m^2

Inclusion criteria (for rheumatoid arthritis patients):

- Healthy male and surgically sterilized or post-menopausal female subjects 18 to 65 years of age
- Fulfilled 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis per Investigator judgement
- Treatment with a stable oral rheumatoid arthritis treatment regimen for ≥ 4 weeks before randomization
- Systemic corticosteroids allowed if on a stable dose (≤ 10 mg/day of prednisone or equivalent) ≥ 4 weeks prior to randomization
- Subjects taking non-steroidal anti-inflammatory drugs (NSAIDs) (cyclooxygenase [COX]-1 or COX-2 inhibitors) as part of their rheumatoid arthritis therapy must have been on a stable dose for at least 4 weeks before randomization

Exclusion criteria (for healthy subjects):

- History of hypersensitivity to vaccines, the study drug, or to drugs of similar chemical classes (i.e., biologic agents)
- Abnormal hematology, coagulation or inflammatory lab results
- History or evidence of tuberculosis.

Exclusion criteria (for rheumatoid arthritis patients):

- Use of anti-TNF or other biologics in previous 3 months
- Any intra-articular injection therapy (e.g., corticosteroid, hyaluronan) required for treatment of acute rheumatoid arthritis flare within 4 weeks before randomization
- Previous treatment with a B cell-depleting biologic agent or any other immunomodulatory biologic agent within 5 half-lives (experimental or approved)
- Current treatment with cyclophosphamide
- Autoimmune disease other than rheumatoid arthritis
- Adult juvenile rheumatoid arthritis
- Rheumatoid arthritis functional status class IV according to the ACR 1991 revised criteria

Participant Flow Table

	CFZ533 0.03 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 10 mg/kg IV RA N=6 n (%)	CFZ533 30 mg/kg IV RA N=4 n (%)	CFZ533 3 mg/kg SC NC-HVs N=6 n (%)	CFZ533 3 mg/kg IV C-HVs N=6 n (%)	Placebo in HVs N=14 n (%)	Placebo in RA patients N=10 n (%)	Total N=76 n (%)
Subjects												
Completed	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	5 (83.3)	3 (75.0)	6 (100.0)	6 (100.0)	14 (100.0)	9 (90.0)	71 (93.4)
Discontinued	1 (16.7)	0	0	0	1 (16.7)	1 (16.7)	1 (25.0)	0	0	0	1 (10.0)	5 (6.6)
Main cause of discontinuation												
Administrative problems	1 (16.7)	0	0	0	1 (16.7)	0	1 (25.0)	0	0	0	1 (10.0)	4 (5.3)
Subject withdrew consent	0	0	0	0	0	1 (16.7)	0	0	0	0	0	1 (1.3)

NC-HVs = non-Chinese healthy volunteers; C-HV = Chinese healthy volunteers; RA = patients with rheumatoid arthritis

Baseline Characteristics

		CFZ533 0.03 mg/kg IV NC-HVs N=6	CFZ533 0.1 mg/kg IV NC-HVs N=6	CFZ533 0.3 mg/kg IV NC-HVs N=6	CFZ533 1 mg/kg IV NC-HVs N=6	CFZ533 3 mg/kg IV NC-HVs N=6	CFZ533 10 mg/kg IV RA N=6	CFZ533 30 mg/kg IV RA N=4	CFZ533 3 mg/kg SC NC-HVs N=6	CFZ533 3 mg/kg IV C-HVs N=6	Placebo in HVs N=14	Placebo in RA patients N=10	Total N=76
Age (years)	Mean(SD)	28.5 (6.16)	31.3 (6.56)	36.7 (11.09)	37.0 (11.61)	37.0 (8.10)	58.3 (8.87)	56.3 (11.03)	32.5 (8.50)	28.2 (2.79)	38.4 (8.64)	58.5 (6.49)	40.6 (13.48)
	Median	27.5	33.5	38.5	34.0	37.5	63.0	60.5	28.0	27.5	38.0	60.5	37.5
	Range	23-40	19-38	20-50	25-52	26-48	46-65	40-64	27-48	25-32	28-51	45-65	19-65
Sex - n(%)	Male	5 (83.3)	6 (100.0)	4 (66.7)	5 (83.3)	5 (83.3)	0	0	5 (83.3)	6 (100.0)	10 (71.4)	1 (10.0)	47(61.8)
	Female	1 (16.7)	0	2 (33.3)	1 (16.7)	1 (16.7)	6 (100.0)	4 (100.0)	1 (16.7)	0	4 (28.6)	9 (90.0)	29(38.2)
Race - n%	Caucasian	5 (83.3)	4 (66.7)	4 (66.7)	6 (100.0)	6 (100.0)	5 (83.3)	4 (100.0)	6 (100.0)	0	11 (78.6)	10 (100.0)	61(80.3)
	Black	0	1 (16.7)	2 (33.3)	0	0	1 (16.7)	0	0	0	1 (7.1)	0	5(6.6)
	Asian	1 (16.7)	1 (16.7)	0	0	0	0	0	0	6 (100.0)	2 (14.3)	0	10(13.2)
Ethnicity - n(%)	Hispanic/Latino	0	0	0	0	1 (16.7)	3 (50.0)	2 (50.0)	2 (33.3)	0	2 (14.3)	4 (40.0)	14(18.4)
	Chinese	0	0	0	0	0	0	0	0	6 (100.0)	2 (14.3)	0	8(10.5)
	Indian (Indian subcontinent)	1 (16.7)	0	0	0	0	0	0	0	0	0	0	1(1.3)
	Other	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)	3 (50.0)	2 (50.0)	4 (66.7)	0	10 (71.4)	6 (60.0)	53(69.7)
Weight (kg)	Mean(SD)	77.9(11.82)	79.8(4.18)	75.6(16.83)	82.3(5.07)	86.9(14.16)	79.3(14.41)	86.2(12.88)	86.9(2.76)	72.5(6.73)	78.6(13.97)	81.4(11.01)	80.3(11.57)
	Median	75.9	81.1	79.9	80.3	84.0	78.2	82.0	87.3	72.3	80.2	82.3	80.6
	Range	66-99	74-85	54-97	78-91	72-109	61-103	77-105	82-90	62-82	54-101	63-97	54-109
Height (cm)	Mean(SD)	171.0(8.25)	176.7(5.09)	169.2(14.62)	171.3(4.97)	178.2(5.98)	160.5(6.72)	162.3(2.99)	178.3(7.47)	174.8(4.36)	174.0(8.82)	164.0(4.42)	171.1(9.07)
	Median	168.5	176.0	176.0	173.0	178.5	158.5	162.0	178.5	175.0	177.5	163.0	172.0
	Range	162-185	171-184	147-184	163-176	170-186	154-173	159-166	167-187	169-179	155-184	158-174	147-187

NC-HVs = non-Chinese healthy volunteers; C-HV = Chinese healthy volunteers; RA = patients with rheumatoid arthritis

Summary of Pharmacokinetics and Immunogenicity

Primary Outcome Result(s) Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Summary of plasma CFZ533 PK parameters in non-Chinese healthy subjects

Parameter	Statistic	0.03 mg/kg IV	0.1 mg/kg IV	0.3 mg/kg IV	1 mg/kg IV	3 mg/kg IV	3 mg/kg SC
Cmax (µg/mL)	N	6	6	6	6	6	6
	Mean	0.0753	0.603	4.76	23.0	82.5	24.9
	CV (%) mean	24.8	61.0	19.0	11.4	14.9	33.8
Tmax (day)	N	6	6	6	6	6	6
	Median	0.0380	0.0810	0.0810	0.166	0.166	3.0
AUClast (day*µg/mL)	N	6	6	6	6	6	6
	Mean	0.00264	0.113	5.88	72.8	572	378
	CV (%) mean	100.1	155.8	48.0	17.5	11.4	38.5

Summary of plasma CFZ533 PK parameters in Chinese healthy subjects and patients with rheumatoid arthritis

Parameter	Statistic	3 mg/kg IV Chinese HVs	10 mg/kg IV RA	30 mg/kg IV RA
Cmax (µg/mL)	N	6	6	4
	Mean	83.6	343	848
	CV (%) mean	19.0	16.7	23.7
Tmax (day)	N	6	6	4
	Median	0.250	0.170	0.250
AUClast (day*µg/mL)	N	6	6	4
	Mean	650	3340	16800
	CV (%) mean	27.1	32.2	22.9

Summary of immunogenicity data: Presence of anti-CFZ533 antibodies

	CFZ533 0.03 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 10 mg/kg IV RA N=6 n (%)	CFZ533 30 mg/kg IV RA N=4 n (%)	CFZ533 3 mg/kg SC NC-HVs N=6 n (%)	CFZ533 3 mg/kg IV C-HVs N=6 n (%)	Placebo in HVs N=14 n (%)	Placebo in RA patients N=10 n (%)
Subjects with detectable ADA	0	0	0	1 (16.7)	0	0	0	0	0	0	0

ADA = anti-drug antibodies; NC-HVs = non-Chinese healthy volunteers; C-HV = Chinese healthy volunteers; RA = patients with rheumatoid arthritis

Actual titer in single subject who had detectable anti-CFZ533 antibodies

Treatment	Subject	Day	Presence of Antibodies?	Titer
CFZ533 1 mg/kg IV	1001/5137	Day 1	No	-
		Day 22	No	-
		Day 29	No	-
		Day 43	No	-
		Day 57	Yes	92.6
		Day 71	Yes	232.3

Values account for a minimal required dilution of 1:5

Presence of antibodies was not associated with any immune-related safety signals.

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Incidence of AEs by primary system organ class – n (percent) of subjects (Comparison A)

	CFZ533 0.03 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg SC NC-HVs N=6 n (%)	Placebo NC-HVs N=12 n (%)	Total N=48 n (%)
Subjects with AE(s)	5 (83.3)	4 (66.7)	6 (100.0)	5 (83.3)	3 (50.0)	5 (83.3)	8 (66.7)	36 (75.0)
System organ class								
Nervous system disorders	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	6 (50.0)	14 (29.2)
Respiratory, thoracic and mediastinal disorders	2 (33.3)	2 (33.3)	1 (16.7)	0	2 (33.3)	4 (66.7)	2 (16.7)	13 (27.1)
General disorders and administration site conditions	1 (16.7)	0	4 (66.7)	1 (16.7)	2 (33.3)	1 (16.7)	2 (16.7)	11 (22.9)
Infections and infestations	0	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	0	1 (8.3)	7 (14.6)
Musculoskeletal and connective tissue disorders	2 (33.3)	0	0	2 (33.3)	0	1 (16.7)	2 (16.7)	7 (14.6)
Gastrointestinal disorders	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0	1 (16.7)	1 (8.3)	6 (12.5)
Injury, poisoning and procedural complications	0	1 (16.7)	0	1 (16.7)	0	1 (16.7)	1 (8.3)	4 (8.3)
Skin and subcutaneous tissue disorders	0	1 (16.7)	1 (16.7)	0	0	0	1 (8.3)	3 (6.3)
Eye disorders	0	0	0	1 (16.7)	0	0	1 (8.3)	2 (4.2)
Investigations	1 (16.7)	0	0	0	0	0	0	1 (2.1)
Metabolism and nutrition disorders	1 (16.7)	0	0	0	0	0	0	1 (2.1)
Psychiatric disorders	0	0	0	0	1 (16.7)	0	0	1 (2.1)
Renal and urinary disorders	0	0	0	1 (16.7)	0	0	0	1 (2.1)

Incidence of AEs by primary system organ class – n (percent) of subjects (Comparison B)

	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	Placebo NC-HVs N=2 n (%)	CFZ533 3 mg/kg IV C-HVs N=6 n (%)	Placebo C-HVs N=2 n (%)	Total N=16 n (%)
Subjects with AE(s)	3 (50.0)	1 (50.0)	5 (83.3)	0	9 (56.3)
System organ class					
Infections and infestations	2 (33.3)	0	1 (16.7)	0	3 (18.8)
Metabolism and nutrition disorders	0	0	3 (50.0)	0	3 (18.8)
Respiratory, thoracic and mediastinal disorders	2 (33.3)	1 (50.0)	0	0	3 (18.8)
General disorders and administration site conditions	2 (33.3)	0	0	0	2 (12.5)
Investigations	0	0	2 (33.3)	0	2 (12.5)
Nervous system disorders	1 (16.7)	1 (50.0)	0	0	2 (12.5)
Gastrointestinal disorders	0	1 (50.0)	0	0	1 (6.3)
Psychiatric disorders	1 (16.7)	0	0	0	1 (6.3)

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Incidence of AEs by primary system organ class – n (percent) of subjects (Comparison C)

	CFZ533 10 mg/kg IV RA N=6 n (%)	CFZ533 30 mg/kg IV RA N=4 n (%)	Placebo RA N=10 n (%)	Total N=20 n (%)
Subjects with AE(s)	6 (100.0)	4 (100.0)	9 (90.0)	19 (95.0)
System organ class				
Infections and infestations	4 (66.7)	2 (50.0)	6 (60.0)	12 (60.0)
Gastrointestinal disorders	2 (33.3)	0	4 (40.0)	6 (30.0)
Nervous system disorders	1 (16.7)	2 (50.0)	3 (30.0)	6 (30.0)
Investigations	1 (16.7)	0	2 (20.0)	3 (15.0)
Metabolism and nutrition disorders	1 (16.7)	0	2 (20.0)	3 (15.0)
Musculoskeletal and connective tissue disorders	1 (16.7)	1 (25.0)	1 (10.0)	3 (15.0)
Skin and subcutaneous tissue disorders	0	0	3 (30.0)	3 (15.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (25.0)	1 (10.0)	2 (10.0)
Psychiatric disorders	0	1 (25.0)	1 (10.0)	2 (10.0)
Respiratory, thoracic and mediastinal disorders	0	1 (25.0)	1 (10.0)	2 (10.0)
Blood and lymphatic system disorders	0	0	1 (10.0)	1 (5.0)
Cardiac disorders	0	0	1 (10.0)	1 (5.0)
General disorders and administration site conditions	0	0	1 (10.0)	1 (5.0)
Injury, poisoning and procedural complications	0	0	1 (10.0)	1 (5.0)
Renal and urinary disorders	0	0	1 (10.0)	1 (5.0)

Arranged in descending order of frequency (in total group) and by system organ class.

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

Incidence of AEs reported by >5% subjects, by preferred term n(percent) of subjects (Comparison A)

	CFZ533 0.03 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 0.3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 1 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	CFZ533 3 mg/kg SC NC-HVs N=6 n (%)	Placebo NC-HVs N=12 n (%)	Total N=48 n (%)
Subjects with AE(s)	5 (83.3)	4 (66.7)	6 (100.0)	5 (83.3)	3 (50.0)	5 (83.3)	8 (66.7)	36 (75.0)
Preferred term								
Headache	3 (50.0)	0	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	6 (50.0)	13 (27.1)
Injection site pain	1 (16.7)	0	2 (33.3)	0	2 (33.3)	0	2 (16.7)	7 (14.6)
Oropharyngeal pain	1 (16.7)	1 (16.7)	0	0	0	3 (50.0)	1 (8.3)	6 (12.5)
Sinus congestion	1 (16.7)	0	0	0	1 (16.7)	2 (33.3)	1 (8.3)	5 (10.4)
Musculoskeletal pain	2 (33.3)	0	0	0	0	1 (16.7)	1 (8.3)	4 (8.3)
Rhinorrhoea	0	1 (16.7)	1 (16.7)	0	0	1 (16.7)	1 (8.3)	4 (8.3)
Back pain	1 (16.7)	0	0	0	0	1 (16.7)	1 (8.3)	3 (6.3)
Cough	1 (16.7)	0	0	0	0	1 (16.7)	1 (8.3)	3 (6.3)
Nausea	1 (16.7)	1 (16.7)	1 (16.7)	0	0	0	0	3 (6.3)
Pain in extremity	1 (16.7)	0	0	1 (16.7)	0	1 (16.7)	0	3 (6.3)

Arranged in descending order of frequency (in total group) and by preferred term.

Incidence of AEs by preferred term n(percent) of subjects (Comparison B)

	CFZ533 3 mg/kg IV NC-HVs N=6 n (%)	Placebo NC-HVs N=2 n (%)	CFZ533 3 mg/kg IV C-HVs N=6 n (%)	Placebo C-HVs N=2 n (%)	Total N=16 n (%)
Subjects with AE(s)	3 (50.0)	1 (50.0)	5 (83.3)	0	9 (56.3)
Preferred term					
Headache	1 (16.7)	1 (50.0)	0	0	2 (12.5)
Hyperglycaemia	0	0	2 (33.3)	0	2 (12.5)
Injection site pain	2 (33.3)	0	0	0	2 (12.5)
Abnormal weight gain	0	0	1 (16.7)	0	1 (6.3)
Anxiety	1 (16.7)	0	0	0	1 (6.3)
Blood bilirubin increased	0	0	1 (16.7)	0	1 (6.3)
Blood triglycerides increased	0	0	1 (16.7)	0	1 (6.3)
Cough	0	1 (50.0)	0	0	1 (6.3)
Gamma-glutamyltransferase increased	0	0	1 (16.7)	0	1 (6.3)
Herpes zoster	0	0	1 (16.7)	0	1 (6.3)
Nasopharyngitis	1 (16.7)	0	0	0	1 (6.3)
Oral herpes	1 (16.7)	0	0	0	1 (6.3)
Productive cough	1 (16.7)	0	0	0	1 (6.3)
Respiratory tract congestion	1 (16.7)	0	0	0	1 (6.3)
Sinus congestion	1 (16.7)	0	0	0	1 (6.3)
Toothache	0	1 (50.0)	0	0	1 (6.3)

Arranged in descending order of frequency (in total group) and by preferred term.

Incidence of AEs reported by >5% subjects by preferred term n(percent) of subjects (Comparison C)

	CFZ533 10 mg/kg IV RA N=6 n (%)	CFZ533 30 mg/kg IV RA N=4 n (%)	Placebo RA N=10 n (%)	Total N=20 n (%)
Subjects with AE(s)	6 (100.0)	4 (100.0)	9 (90.0)	19 (95.0)
Preferred term				
Upper respiratory tract infection	2 (33.3)	2 (50.0)	3 (30.0)	7 (35.0)
Urinary tract infection	1 (16.7)	0	4 (40.0)	5 (25.0)
Headache	1 (16.7)	1 (25.0)	2 (20.0)	4 (20.0)
Nasopharyngitis	2 (33.3)	1 (25.0)	0	3 (15.0)
Nausea	1 (16.7)	0	2 (20.0)	3 (15.0)
Bronchitis	0	0	2 (20.0)	2 (10.0)
Hypokalaemia	1 (16.7)	0	1 (10.0)	2 (10.0)
Vomiting	2 (33.3)	0	0	2 (10.0)

Arranged in descending order of frequency (in total group) and by preferred term.

Subjects experiencing AEs that were suspected to be related to study drug

Treatment group	Preferred term for adverse event	Study day	Severity
CFZ533 0.03 mg/kg IV in non-Chinese healthy subjects	Body temperature increased	20	Grade 1
	Sinus congestion	20	Grade 1
	Headache	1	Grade 2
	Nausea	2	Grade 1
	Headache	6	Grade 1
	Oropharyngeal pain	7	Grade 1
	Decreased appetite	8	Grade 1
	Respiratory tract congestion	11	Grade 1
	Productive cough	12	Grade 1
	Cough	18	Grade 1
CFZ533 0.1 mg/kg IV in non-Chinese healthy subjects	Tooth infection	71	Grade 1
	Papule	12	Grade 1
	Papule	31	Grade 1
	Oropharyngeal pain	53	Grade 1
	Papule	135	Grade 1
	Nausea	1	Grade 1
CFZ533 0.3 mg/kg IV in non-Chinese healthy subjects	Nausea	66	Grade 1
	Diarrhoea	66	Grade 1
	Pharyngitis	71	Grade 1
	Pyrexia	71	Grade 1
CFZ533 1 mg/kg IV in non-Chinese healthy subjects	Pain in jaw	4	Grade 1
	Feeling hot	3	Grade 1
CFZ533 3 mg/kg IV in non-Chinese healthy subjects	Injection site pain	4	Grade 1

Treatment group	Preferred term for adverse event	Study day	Severity
	Injection site pain	4	Grade 1
CFZ533 3 mg/kg IV in Chinese healthy subjects	Herpes zoster	16	Grade 1
CFZ533 10 mg/kg IV in rheumatoid arthritis patients	Headache	1	Grade 1
CFZ533 30 mg/kg IV in rheumatoid arthritis patients	Myalgia	2	Grade 1
	Oropharyngeal pain	2	Grade 1
	Nasopharyngitis	41	Grade 1
Placebo in healthy subjects	Tinea pedis	40	Grade 1
	Headache	2	Grade 1
	Myalgia	3	Grade 1
	Oropharyngeal pain	70	Grade 1
Placebo in rheumatoid arthritis patients	Aspartate aminotransferase increased	15	Grade 1

Serious Adverse Events and Deaths

	CFZ533 - HVs (0.03 to 3 mg/kg IV and 3 mg/kg SC) N=42 n (%)	CFZ533 - RA (10 mg/kg IV) N=6 n (%)	CFZ533 - RA (30 mg/kg IV) N=4 n (%)	Placebo - HV and RA N=24 n (%)	Total N=76 n (%)
Number (%) Subjects with serious of other significant events					
Death	0	0	0	0	0
SAE(s)	0	0	1 (25.0)	1 (4.2)	2 (2.6)
Discontinued due to SAE(s)	0	0	0	0	0

	CFZ533 - HVs (0.03 to 3 mg/kg IV and 3 mg/kg SC) N=42 n (%)	CFZ533 - RA (10 mg/kg IV) N=6 n (%)	CFZ533 - RA (30 mg/kg IV) N=4 n (%)	Placebo - HV and RA N=24 n (%)	Total N=76 n (%)

HVs = healthy volunteers; RA = patients with rheumatoid arthritis

Other Relevant Findings: N/A

Conclusion:

CFZ533 was safe and well tolerated following single doses up to 3 mg/kg IV and SC in healthy subjects and following single doses up to 30 mg/kg IV in patients with rheumatoid arthritis.

In healthy subjects as well as in patients with rheumatoid arthritis, after single IV or SC administration, CFZ533 PK profiles were consistent with target-mediated disposition resulting in non-linear PK profiles.

The disposition of CFZ533 in Chinese healthy subjects was similar as for non-Chinese subjects.

After SC administration in healthy subjects, CFZ533 was rapidly absorbed and distributed in line with what was expected for a typical IgG1 antibody in humans.

One subject at 1 mg/kg IV CFZ533 developed specific anti-drug antibodies (ADAs) to CFZ533 at 6 weeks after CFZ533 dosing. The presence of ADAs in this subject did not compromise exposure, and was not associated with an immune related safety signal. This corresponds to an ADA incidence of 2%.

There was no evidence of an increased risk of infections AEs during the 6-month follow-up period after single doses of CFZ533 up to 30 mg/kg.

There was no evidence of thromboembolic complications following single doses of CFZ533 up to 30 mg/kg.

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