NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Iscalimab

Trial Indication(s)

Myasthenia gravis

Protocol Number

CCFZ533X2204

Protocol Title

A multi-center, randomized, double-blind, placebo-controlled, parallel group study to preliminarily evaluate the safety, tolerability, pharmacokinetics and efficacy of CFZ533 in patients with moderate to severe myasthenia gravis

Clinical Trial Phase

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: September 2015 (Actual)
Primary Completion Date: July 2017 (Actual)
Study Completion Date: December 2017 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a randomized double-blind, placebo controlled, non-confirmatory study to preliminarily evaluate the safety, tolerability, PK/PD, and efficacy of 10 mg/kg IV CFZ533 administered every four weeks (q4w) over a 24 week treatment period in patients with moderate to severe MG. The investigational drug or placebo was administered in addition to standard of care therapy for MG.

Centers

14 centers in 5 countries: Denmark(2), Germany(2), Taiwan(3), Canada(2), Russia(5)

Objectives:

Primary objectives:

- To evaluate the safety and tolerability of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG throughout the study
- To evaluate the efficacy of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG after 24 weeks of treatment.

Secondary objectives

- To evaluate the efficacy of IV CFZ533 using relevant MG related outcome measures throughout the 24 weeks treatment period.
- To evaluate the decay in efficacy of IV CFZ533 using relevant MG related outcome measures throughout the 24 weeks follow-up period.
- To evaluate changes in patient’s quality of life (QOL) throughout the 24 weeks treatment period.
- To evaluate the PK of 2-hour IV infusion of CFZ533 at 10 mg/kg administered q4w for 6 doses.

- To evaluate the PD of CFZ533 (extent/duration of target engagement through sCD40 in plasma and CD40 saturation on whole blood B cells,).
- To assess immunogenicity in CFZ533-treated patients and in placebo-treated patients (pre-existing anti-drug antibodies).

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

The investigational drug, (CFZ533) and placebo were prepared by Novartis and supplied to the Investigative site as open-label bulk medication. CFZ533 was provided as lyophilisate in vial (150 mg) and the placebo as liquid in vials.

Statistical Methods

The primary efficacy variable was the change from baseline in QMG score after 24 weeks of treatment (at Week 25 visit). The baseline value was the predose assessment on Day 1. It was assumed that the change from baseline in QMG score was normally distributed. The changes from baseline in QMG scores at Week 25 were analyzed using a Bayesian model. The model investigated effects for treatment (CFZ533 or placebo) and baseline QMG score.

A difference of 3 points on the mean change in QMG score between CFZ533 and placebo was deemed a clinical meaningful effect.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
1. Diagnosis of MG class IIa to IVa inclusive (Myasthenia Gravis Foundation of America Clinical Classification).
2. Quantitative Myasthenia Gravis (QMG) score of 10 or greater. If the QMG score is < 15 no more than 4 points may be derived from items 1 or 2 (ocular motility disturbance and ptosis).
3. Documented history of acetylcholine receptor (AChR) or Muscle Specific Kinase (MuSK) antibody positive.
4. Only one immunosuppressant or immunomodulatory drug at a stable dose is allowed during the study (i) azathioprine and mycophenolate mofetil must be stable for at least 4 months prior to randomization (ii) cyclosporine must be stable for at least 3 months prior to randomization.
5. If the patient is on oral corticosteroids, methotrexate or tacrolimus at screening, the dose must be stable for at least 1 month prior to randomization.
6. If the patient is on cholinesterase inhibitors at screening, the dose must be stable for at least 2 weeks prior to randomization.
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, may be included in the study if they are using highly effective methods of contraception during the study and for 12 weeks after study treatment.

Exclusion Criteria:

1. MGFA grade I, IVb, or V disease.
2. Documented presence of unresected thymoma.
3. Patients having undergone thymectomy or thymo thymectomy (resection of thymoma) within 6 months of screening.
4. Patients having received any of the following treatments prior to randomization:
a. IVIg or plasma exchange within 8 weeks;
b. oral or IV cyclosphosphamide treatment within 3 months;
c. IV corticosteroid bolus (dose higher than 1 mg/kg) within 3 months;
d. belimumab within 6 months. For patients who received belimumab earlier, B cell count should be within normal range;
e. rituximab within 12 months. For patients who received rituximab earlier, B cell count should be within normal range;
f. any other biologic or an investigational drug within 1 month or five times thehalf-life, whichever is longer.
g. Live vaccines within 4 weeks of study drug infusion.
5. Patients who are at significant risk for TE as judged by the investigator or have any one of the following:
a. History of either thrombosis or 3 or more spontaneous abortions with or without the presence of anti-cardiolipin autoantibodies;
b. Presence of prolonged partial thromboplastin time (PTT).

Participant Flow Table

Overall Study

	CFZ533	Placebo
Started	22	22
Completed	17	17
Not Completed	5	5
abnormal lab value	2	0

subject / guardian decision	1	3
Lost to Follow-up	1	0
Death	0	2
Adverse Event	1	0

Baseline Characteristics

	CFZ533	Placebo	Total
Number of Participants [units: participants]	22	22	44
Age Continuous (units: years) Mean ± Standard Deviation			
	44.7±13.54	43.3±13.92	44.0±13.59
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	12	16	28
Male	10	6	16
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)			
caucasian	19	16	35
Asian (Chinese)	3	5	8
other	0	1	1

Summary of Efficacy

Primary Outcome Result(s)

Mean change from baseline in the Quantitative Myastenia Gravis (QMG) score at week 25. Posterior Median was used as measure type.

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	18	18
Mean change from baseline in the Quantitative Myastenia Gravis (QMG) score at week 25. Posterior Median was used as measure type. (units: score) Median (90% Confidence Interval)		
	-4.07 (-5.67 to -2.47)	-2.93 (-4.53 to -1.33)

Statistical Analysis

Groups	CFZ533, Placebo	Primary analysis was performed on the PD analysis set. Changes from baseline in QMG scores at Week 25 were analyzed using a Bayesian model. The model

		investigated effects for treatment (CFZ533 or placebo) and baseline QMG score. A difference of 3 points on the mean change in QMG score between CFZ533 and placebo was deemed a clinical meaningful effect.

Method	Other bayesian
Other estimate of contrast posterior median	-1.14
90 % Confidence Interval 2-Sided	-3.41 to 1.14

Secondary Outcome Result(s)

Mean changes from baseline in the Myasthenia Gravis Composite (MGC) score. Posterior Median was used as measure type.

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	18	18
Mean changes from baseline in the Myasthenia Gravis Composite (MGC) score. Posterior Median was used as measure type. (units: score) Median (90% Confidence Interval)		

	-8.00 (-9.83 to -6.16)	-5.62 (-7.45 to -3.78)

Proportion of patients with improvement or worsening by ≥ 3 points in the QMG score

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	18	19
Proportion of patients with improvement or worsening by ≥ 3 points in the QMG score (units: participants) Count of Participants (Not Applicable)		
improvement by ≥ 3 points in the QMG score	10	9
worsening by ≥ 3 points in the QMG score	2	2

Proportion of patients intolerant to steroid taper

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	22	22
Proportion of patients intolerant to steroid taper (units: participants) Count of Participants (Not Applicable)		
	NA[]	NA[]

Proportion of patients who discontinued due to inefficacy or worsening

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	22	22
Proportion of patients who discontinued due to inefficacy or worsening (units: participants) Count of Participants (Not Applicable)		
	0	0

Mean change from baseline in the Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL)

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	19	18
Mean change from baseline in the Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL) (units: score) Mean ± Standard Deviation		
	-2.6 ± 2.97	-1.1 ± 3.23

Mean changes from baseline in the QMG score at week 49

	CFZ533	Placebo

Number of Participants Analyzed [units: participants]	18	19
Mean changes from baseline in the QMG score at week 49 (units: change from baseline) Mean ± Standard Deviation		
	-2.9 ± 5.16	-2.6 ± 4.30

Mean change from baseline in the Myasthenia Gravis Quality of Life (MG QOL-15)

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	19	19
Mean change from baseline in the Myasthenia Gravis Quality of Life (MG QOL-15) (units: score) Mean ± Standard Deviation		
	-9.7 ± 11.0	-6.7 ± 10.86

Free CD40 on B cells

	CFZ533	Placebo
Number of Participants Analyzed [units: participants]	22	22

Free CD40 on B cells (units: MESF) Mean ± Standard Deviation		
Free CD40 on B cells week 1 predose	34242.9 ± 18455.80	31025.9 ± 16138.97
Free CD40 on B cells week 25	5259.1 ± 11341.57	24908.3 ± 5022.03

Total soluble CD40 (sCD40) in plasma

	CFZ533	**Placebo**
Number of Participants Analyzed [units: participants]	22	22
Total soluble CD40 (sCD40) in plasma (units: ng/ml) Mean ± Standard Deviation		
week 1	0.1778 ± 0.13077	0.1577 ± 0.17243
week 25	191.1278 ± 69.67597	0.1163 ± 0.18298

plasma CFZ533 concentration at steady state conditions (Week 17)

	CFZ533	**Placebo**
Number of Participants Analyzed [units: participants]	18	18
plasma CFZ533 concentration at steady state conditions (Week 17) (units: microg/mL)		

Mean ± Standard Deviation		
	120 ± 40.5	0 ± 0

Summary of Safety

Safety Results

All-Cause Mortality

	CFZ533 10 mg/kg IV infusion N = 22	Placebo IV infusion N = 22
Total participants affected	0 (0.00%)	2 (9.09%)

Serious Adverse Events by System Organ Class

Time Frame	Timeframe for AE
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	CFZ533 10 mg/kg IV infusion N = 22	Placebo IV infusion N = 22
Total participants affected	7 (31.82%)	4 (18.18%)
Blood and lymphatic system disorders		
Febrile neutropenia	1 (4.55%)	0 (0.00%)
Cardiac disorders		
Myocardial ischaemia	0 (0.00%)	1 (4.55%)
Eye disorders		
Glaucoma	1 (4.55%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal pain upper	1 (4.55%)	0 (0.00%)
Constipation	1 (4.55%)	0 (0.00%)
General disorders and administration site conditions		
Pyrexia	1 (4.55%)	0 (0.00%)
Hepatobiliary disorders		
Hepatitis toxic	0 (0.00%)	1 (4.55%)
Infections and infestations		
Influenza	2 (9.09%)	0 (0.00%)
Pneumonia	1 (4.55%)	0 (0.00%)

Nervous system disorders		
Brachial plexopathy	0 (0.00%)	1 (4.55%)
Myasthenia gravis	2 (9.09%)	1 (4.55%)
Myasthenia gravis crisis	1 (4.55%)	0 (0.00%)
Radial nerve palsy	0 (0.00%)	1 (4.55%)

Other Adverse Events by System Organ Class

Time Frame	Timeframe for AE
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	CFZ533 10 mg/kg IV infusion N = 22	**Placebo IV infusion N = 22**
Total participants affected	20 (90.91%)	21 (95.45%)
Blood and lymphatic system disorders		
Anaemia	0 (0.00%)	2 (9.09%)
Iron deficiency anaemia	1 (4.55%)	0 (0.00%)
Leukocytosis	1 (4.55%)	0 (0.00%)
Leukopenia	2 (9.09%)	2 (9.09%)

Lymphocytosis	0 (0.00%)	1 (4.55%)
Lymphopenia	1 (4.55%)	2 (9.09%)
Neutropenia	1 (4.55%)	1 (4.55%)
Neutrophilia	1 (4.55%)	0 (0.00%)
Cardiac disorders		
Angina pectoris	0 (0.00%)	1 (4.55%)
Atrial fibrillation	1 (4.55%)	0 (0.00%)
Palpitations	0 (0.00%)	1 (4.55%)
Congenital, familial and genetic disorders		
Von Willebrand's disease	1 (4.55%)	0 (0.00%)
Eye disorders		
Cataract	0 (0.00%)	1 (4.55%)
Vision blurred	1 (4.55%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal pain	0 (0.00%)	1 (4.55%)
Abdominal pain upper	0 (0.00%)	1 (4.55%)
Dental caries	0 (0.00%)	1 (4.55%)
Diarrhoea	1 (4.55%)	2 (9.09%)
Food poisoning	1 (4.55%)	0 (0.00%)
Gastroduodenitis	1 (4.55%)	0 (0.00%)
Gingival bleeding	0 (0.00%)	1 (4.55%)
Nausea	3 (13.64%)	2 (9.09%)
Pancreatitis chronic	0 (0.00%)	1 (4.55%)

General disorders and administration site conditions		
Asthenia	0 (0.00%)	2 (9.09%)
Chills	0 (0.00%)	1 (4.55%)
Discomfort	0 (0.00%)	1 (4.55%)
Fatigue	2 (9.09%)	0 (0.00%)
Feeling cold	1 (4.55%)	0 (0.00%)
Hyperthermia	0 (0.00%)	1 (4.55%)
Influenza like illness	1 (4.55%)	0 (0.00%)
Infusion site bruising	0 (0.00%)	1 (4.55%)
Malaise	0 (0.00%)	1 (4.55%)
Non-cardiac chest pain	1 (4.55%)	0 (0.00%)
Pyrexia	0 (0.00%)	2 (9.09%)
Hepatobiliary disorders		
Hepatitis toxic	0 (0.00%)	1 (4.55%)
Infections and infestations		
Acute sinusitis	0 (0.00%)	1 (4.55%)
Bronchitis	1 (4.55%)	0 (0.00%)
Conjunctivitis	0 (0.00%)	1 (4.55%)
Cystitis	1 (4.55%)	2 (9.09%)
Ear infection	0 (0.00%)	1 (4.55%)
Folliculitis	0 (0.00%)	1 (4.55%)
Gastrointestinal infection	1 (4.55%)	0 (0.00%)
Herpes virus infection	0 (0.00%)	1 (4.55%)
Herpes zoster	0 (0.00%)	2 (9.09%)

Influenza	1 (4.55%)	1 (4.55%)
Laryngitis viral	1 (4.55%)	0 (0.00%)
Nasopharyngitis	2 (9.09%)	3 (13.64%)
Oral candidiasis	1 (4.55%)	0 (0.00%)
Oral herpes	1 (4.55%)	1 (4.55%)
Oropharyngeal candidiasis	0 (0.00%)	1 (4.55%)
Pneumonia	2 (9.09%)	1 (4.55%)
Respiratory tract infection	1 (4.55%)	0 (0.00%)
Respiratory tract infection viral	2 (9.09%)	2 (9.09%)
Rhinitis	1 (4.55%)	0 (0.00%)
Skin candida	0 (0.00%)	1 (4.55%)
Systemic infection	1 (4.55%)	0 (0.00%)
Tonsillitis	0 (0.00%)	1 (4.55%)
Tooth infection	1 (4.55%)	0 (0.00%)
Tracheobronchitis	1 (4.55%)	0 (0.00%)
Upper respiratory tract infection	1 (4.55%)	4 (18.18%)
Urinary tract infection	1 (4.55%)	1 (4.55%)
Viral pharyngitis	1 (4.55%)	0 (0.00%)
Vulvovaginal candidiasis	0 (0.00%)	1 (4.55%)
Injury, poisoning and procedural complications		
Ligament rupture	0 (0.00%)	1 (4.55%)
Muscle strain	0 (0.00%)	1 (4.55%)

Procedural headache	0 (0.00%)	1 (4.55%)
Procedural pain	0 (0.00%)	1 (4.55%)
Investigations		
Activated partial thromboplastin time prolonged	1 (4.55%)	0 (0.00%)
Activated partial thromboplastin time shortened	1 (4.55%)	0 (0.00%)
Alanine aminotransferase increased	1 (4.55%)	0 (0.00%)
Blood bicarbonate decreased	0 (0.00%)	1 (4.55%)
Blood creatine phosphokinase increased	0 (0.00%)	1 (4.55%)
Blood creatinine increased	0 (0.00%)	1 (4.55%)
Blood lactate dehydrogenase increased	0 (0.00%)	1 (4.55%)
Blood pressure increased	0 (0.00%)	1 (4.55%)
C-reactive protein increased	1 (4.55%)	0 (0.00%)
Free haemoglobin present	2 (9.09%)	2 (9.09%)
Gamma-glutamyltransferase increased	1 (4.55%)	0 (0.00%)

Prothrombin time prolonged	1 (4.55%)	0 (0.00%)
Weight decreased	1 (4.55%)	0 (0.00%)
Metabolism and nutrition disorders		
Decreased appetite	1 (4.55%)	0 (0.00%)
Dyslipidaemia	1 (4.55%)	0 (0.00%)
Hypercholesterolaemia	1 (4.55%)	0 (0.00%)
Hypoglycaemia	0 (0.00%)	1 (4.55%)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (4.55%)	1 (4.55%)
Arthritis reactive	1 (4.55%)	0 (0.00%)
Joint swelling	0 (0.00%)	1 (4.55%)
Muscle spasms	0 (0.00%)	2 (9.09%)
Muscular weakness	2 (9.09%)	1 (4.55%)
Musculoskeletal pain	0 (0.00%)	1 (4.55%)
Myalgia	1 (4.55%)	0 (0.00%)
Neck pain	1 (4.55%)	0 (0.00%)
Osteochondrosis	0 (0.00%)	1 (4.55%)
Tendonitis	1 (4.55%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Skin papilloma	0 (0.00%)	1 (4.55%)
Nervous system disorders		

Dementia Alzheimer's type	1 (4.55%)	0 (0.00%)
Dizziness	2 (9.09%)	2 (9.09%)
Headache	4 (18.18%)	3 (13.64%)
Migraine	1 (4.55%)	0 (0.00%)
Myasthenia gravis	2 (9.09%)	1 (4.55%)
Nerve compression	0 (0.00%)	1 (4.55%)
Neuralgia	1 (4.55%)	0 (0.00%)
Paraesthesia	1 (4.55%)	0 (0.00%)
Post herpetic neuralgia	0 (0.00%)	1 (4.55%)
Psychiatric disorders		
Depressed mood	1 (4.55%)	0 (0.00%)
Nervousness	1 (4.55%)	0 (0.00%)
Panic attack	0 (0.00%)	1 (4.55%)
Sleep disorder	1 (4.55%)	0 (0.00%)
Renal and urinary disorders		
Calculus urinary	1 (4.55%)	0 (0.00%)
Haematuria	1 (4.55%)	0 (0.00%)
Reproductive system and breast disorders		
Balanoposthitis	0 (0.00%)	1 (4.55%)
Breast pain	0 (0.00%)	1 (4.55%)
Respiratory, thoracic and mediastinal disorders		
Asthma	1 (4.55%)	0 (0.00%)

Cough	1 (4.55%)	0 (0.00%)
Laryngeal inflammation	0 (0.00%)	1 (4.55%)
Nasal congestion	0 (0.00%)	1 (4.55%)
Sinus disorder	1 (4.55%)	0 (0.00%)
Skin and subcutaneous tissue disorders		
Acne	0 (0.00%)	1 (4.55%)
Dermatitis allergic	1 (4.55%)	0 (0.00%)
Erythema	1 (4.55%)	0 (0.00%)
Hyperhidrosis	0 (0.00%)	1 (4.55%)
Pruritus	1 (4.55%)	0 (0.00%)
Rash	0 (0.00%)	1 (4.55%)
Swelling face	1 (4.55%)	0 (0.00%)

Other Relevant Findings

none

Conclusion:

Overall, CFZ533 was safe and well tolerated up to 10 mg/kg IV monthly for 6 months. Pharmacokinetic profiles of CFZ533 were as expected for the 10 mg/kg Q4W IV regimen, suggesting complete CD40 pathway blockade in target tissues. Although there was no difference between CFZ533 and placebo at Week 25, a positive trend both in QMG and MGC was observed in favor of CFZ533 from baseline until Week 13 during treatment period and from Week 29 until Week 37 in follow-up period. The observed trend was more evident during the period up to Week 13 when the dose of steroids therapy was stable. The effect seemed to diminish after Week 13, which might have been attributable to confounding effect of the permitted steroid taper.

Date of Clinical Trial Report

7-Nov-2018