



Clinical trial results:

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

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-000097-35 |
| Trial protocol | DE DK |
| Global end of trial date | 19 December 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 28 December 2018 |
| First version publication date | 28 December 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CCFZ533X2204 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharmaceuticals |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 19 December 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective for the trial were :

- to evaluate the safety and tolerability of intravenous (IV) CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG throughout the study,
- and to evaluate the efficacy of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 29 September 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | Denmark: 7 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Russian Federation: 24 |
| Country: Number of subjects enrolled | Taiwan: 7 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 9 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 40 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 44 patients were randomized to receive either IV CFZ533 or IV placebo, of which 34 patients (77%) completed the study.

Pre-assignment

Screening details:

Safety analysis set, and Full analysis: 44 patients (22 treated with CFZ533 and 22 with placebo)

PK analysis set : 20 patients treated with CFZ533

PD analysis set: 42 patients (20 treated with CFZ533 and 20 with placebo)

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | CFZ533 |

Arm description:

CFZ533 10 mg/kg

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | CFZ533 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

CFZ533 was provided as lyophilisate in vial (150 mg).

CFZ533 was administered as a 10 mg/kg IV infusion given over 2 hours, every 28 days (q4w), for a treatment duration of 24 weeks (six doses).

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo

| | |
|--|---------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The CFZ533 matching placebo was provided as liquid in vials, and was administered as IV infusion over 2 hours, every 28 days (q4w), for a treatment duration of 24 weeks (six doses).

| Number of subjects in period 1 | CFZ533 | Placebo |
|---------------------------------------|--------|---------|
| Started | 22 | 22 |
| Completed | 17 | 17 |
| Not completed | 5 | 5 |
| Adverse event, serious fatal | - | 2 |
| Adverse event, non-fatal | 1 | - |
| subject / guardian decision | 1 | 3 |
| Lost to follow-up | 1 | - |
| abnormal lab value | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | CFZ533 |
|-----------------------|--------|

Reporting group description:

CFZ533 10 mg/kg

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| Reporting group values | CFZ533 | Placebo | Total |
|---|---------|---------|-------|
| Number of subjects | 22 | 22 | 44 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 20 | 20 | 40 |
| From 65-84 years | 2 | 2 | 4 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 44.7 | 43.3 | |
| standard deviation | ± 13.54 | ± 13.92 | - |
| Sex: Female, Male Units: Subjects | | | |
| Female | 12 | 16 | 28 |
| Male | 10 | 6 | 16 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| caucasian | 19 | 16 | 35 |
| Asian (Chinese) | 3 | 5 | 8 |
| other | 0 | 1 | 1 |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | CFZ533 |
| Reporting group description: CFZ533 10 mg/kg | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |

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

| | |
|--|--|
| End point title | Mean change from baseline in the Quantitative Myasthenia Gravis (QMG) score at week 25. Posterior Median was used as measure type. |
| End point description: The QMG score is an established and validated measure of disease severity used in MG trials (Jaretzki et al 2000). This scoring system is based on quantitative testing of sentinel muscle groups by means of a 4 point scale ranging from 0 (no symptoms) to 3 (severe symptoms). The scale measures ocular, bulbar, respiratory, and limb function, grading each finding, and the total score ranges from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits). Its reliability and longitudinal validity have been demonstrated in several studies (Sharshar et al 2000, Bedlack et al 2005). | |
| End point type | Primary |
| End point timeframe: week 25 | |

| End point values | CFZ533 | Placebo | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: score | | | | |
| median (confidence interval 90%) | -4.07 (-5.67 to -2.47) | -2.93 (-4.53 to -1.33) | | |

Statistical analyses

| | |
|--|----------------------------|
| Statistical analysis title | Analysis primary objective |
| Statistical analysis description: The changes from baseline in QMG scores at Week 25 were analyzed using a Bayesian model that investigated effects for CFZ533 or placebo and baseline QMG score. The prior of the difference in changes from baseline between CFZ533 and placebo at week 25 was used to obtain the posterior estimates. Bayesian posterior probabilities at Week 25 were ≥ 0 or ≥ 3 points. A difference of 3 points on the mean change in QMG score was deemed clinically meaningful. | |
| Comparison groups | Placebo v CFZ533 |

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Method | bayesian |
| Parameter estimate | estimate of contrast posterior median |
| Point estimate | -1.14 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -3.41 |
| upper limit | 1.14 |

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

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

End point description:

The MGC score is another key efficacy outcome measure. It is reliable and demonstrates concurrent and longitudinal construct validity in the MG practice care setting (Burns et al 2010). The MGC scale covers 10 important functional domains most frequently involved in patients with MG. The proportion of bulbar and respiratory items reflect the clinical importance of these domains in the disease, and are appropriately weighted. The assessment of each of the 10 test items provides immediate insight into the status of that particular functional domain.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to week 49

| End point values | CFZ533 | Placebo | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: score | | | | |
| median (confidence interval 90%) | -8.00 (-9.83 to -6.16) | -5.62 (-7.45 to -3.78) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Proportion of patients with improvement or worsening by ≥ 3 points in the QMG score |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:
at week 49

| End point values | CFZ533 | Placebo | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 19 | | |
| Units: participants | | | | |
| improvement by ≥ 3 points in the QMG score | 10 | 9 | | |
| worsening by ≥ 3 points in the QMG score | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients intolerant to steroid taper

| | |
|---------------------------------|--|
| End point title | Proportion of patients intolerant to steroid taper |
| End point description: | |
| End point type | Secondary |
| End point timeframe: week 49 | |

| End point values | CFZ533 | Placebo | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 ^[1] | 22 ^[2] | | |
| Units: participants | 0 | 0 | | |

Notes:

[1] - this data was not collected

[2] - this data was not collected

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients who discontinued due to inefficacy or worsening

| | |
|---------------------------------|--|
| End point title | Proportion of patients who discontinued due to inefficacy or worsening |
| End point description: | |
| End point type | Secondary |
| End point timeframe: week 49 | |

| End point values | CFZ533 | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 | 22 | | |
| Units: participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|---|
| End point title | Mean change from baseline in the Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL) |
| End point description: The MG-ADL is an 8-item survey to assess functional performance of daily activities that are sometimes impaired by MG e.g. talking, breathing, swallowing etc. (Muppidi et al 2011). The higher score on MG-ADL scale (0-24 points) indicates worse functional performance of daily activities. | |
| End point type | Secondary |
| End point timeframe: week 25 | |

| End point values | CFZ533 | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 18 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -2.6 (\pm 2.97) | -1.1 (\pm 3.23) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean changes from baseline in the QMG score at week 49

| | |
|---------------------------------|--|
| End point title | Mean changes from baseline in the QMG score at week 49 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: week 49 | |

| End point values | CFZ533 | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 19 | | |
| Units: change from baseline | | | | |
| arithmetic mean (standard deviation) | -2.9 (\pm 5.16) | -2.6 (\pm 4.30) | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|--|
| End point title | Mean change from baseline in the Myasthenia Gravis Quality of Life (MG QOL-15) |
| End point description: The MG-QOL15 is a 15-item survey, completed by MG patients and it is designed to assess some aspects of quality of life (QoL) related to MG (Burns et al 2011) e.g. assesment of mood, eating, speaking, driving a car etc.. The higher score on MG-QOL15 scale (0-60 points) indicates worse QoL. | |
| End point type | Secondary |
| End point timeframe: week 25 | |

| End point values | CFZ533 | Placebo | | |
|--------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 19 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | -9.7 (\pm 11.0) | -6.7 (\pm 10.86) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Free CD40 on B cells

| | |
|--|----------------------|
| End point title | Free CD40 on B cells |
| End point description: CD40 receptor occupancy by CFZ533 in peripheral blood was assessed by flow cytometry analysis, measuring free or total CD40 receptors on whole blood B cells. Free CD40 on CD19-positive B cells, using PE-conjugated CFZ533 whose binding was prevented by bound, unconjugated CFZ533 (drug bound to CD40 on peripheral blood B cells). The more CD40 was occupied by unlabeled CFZ533, the less binding of labeled CFZ533, manifest as a lower mean fluorescence intensity (MFI) of CD40 on B cells. MFI from free CD40 on B cells was converted into Molecules of Equivalent Soluble Fluorochrome (MESF) using PE-MESF beads. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| week 1, week 25 | |

| End point values | CFZ533 | Placebo | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 ^[3] | 22 ^[4] | | |
| Units: MESF | | | | |
| arithmetic mean (standard deviation) | | | | |
| week 1 | 34242.9 (± 18455.80) | 31025.9 (± 16138.97) | | |
| week 25 | 5259.1 (± 11341.57) | 24908.3 (± 5022.03) | | |

Notes:

[3] - 14 participants at week 1, 8 participants at week 25

[4] - 17 participants at week 1, 12 participants at week 25

Statistical analyses

No statistical analyses for this end point

Secondary: Total soluble CD40 (sCD40) in plasma

| | |
|------------------------|--------------------------------------|
| End point title | Total soluble CD40 (sCD40) in plasma |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| week 1, week 25 | |

| End point values | CFZ533 | Placebo | | |
|--------------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 ^[5] | 22 ^[6] | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| week 1 | 0.1778 (± 0.13077) | 0.1577 (± 0.17243) | | |
| week 25 | 191.1278 (± 69.67597) | 0.1163 (± 0.18298) | | |

Notes:

[5] - 21 participants at week 1, 18 participants at week 25

[6] - 20 participants at week 1, 19 participants at week 25

Statistical analyses

No statistical analyses for this end point

Secondary: plasma CFZ533 concentration at steady state conditions

| | |
|------------------------|--|
| End point title | plasma CFZ533 concentration at steady state conditions |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| week 17 | |

| End point values | CFZ533 | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 22 ^[7] | | |
| Units: microg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| week 17 (steady state) | 120 (\pm 4.05) | 0 (\pm 0) | | |

Notes:

[7] - only patients treated with CFZ533, therefore patients treated with placebo were not analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo IV infusion |
|-----------------------|---------------------|

Reporting group description:

Placebo IV infusion

| | |
|-----------------------|-----------------------------|
| Reporting group title | CFZ533 10 mg/kg IV infusion |
|-----------------------|-----------------------------|

Reporting group description:

CFZ533 10 mg/kg IV infusion

| Serious adverse events | Placebo IV infusion | CFZ533 10 mg/kg IV infusion | |
|---|---------------------|-----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 7 / 22 (31.82%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Brachial plexopathy | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 22 (9.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenia gravis crisis | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radial nerve palsy | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis toxic | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 22 (9.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Placebo IV infusion | CFZ533 10 mg/kg IV infusion | |
|--|---------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 22 (95.45%) | 20 / 22 (90.91%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 22 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Discomfort | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 22 (9.09%) | |
| occurrences (all) | 0 | 4 | |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Infusion site bruising | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 2 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 22 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Breast pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Cough | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Nervousness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Activated partial thromboplastin time shortened | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Blood bicarbonate decreased | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Free haemoglobin present | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 2 / 22 (9.09%) | |
| occurrences (all) | 3 | 4 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle strain | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Procedural headache subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Procedural pain subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Congenital, familial and genetic disorders Von Willebrand's disease subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Nervous system disorders Dementia Alzheimer's type subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 3 | 2 / 22 (9.09%) 3 | |
| Headache subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 5 | 4 / 22 (18.18%) 7 | |
| Migraine subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Myasthenia gravis | | | |

| | | | |
|--------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 22 (9.09%) | |
| occurrences (all) | 1 | 2 | |
| Nerve compression | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 2 | |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 22 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 2 / 22 (9.09%) | |
| occurrences (all) | 2 | 2 | |
| Lymphocytosis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 22 (4.55%) | |
| occurrences (all) | 2 | 1 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|--|---------------------|----------------------|--|
| Neutrophilia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Eye disorders | | | |
| Cataract subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Dental caries subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 1 / 22 (4.55%) 1 | |
| Food poisoning subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Gastroduodenitis subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Gingival bleeding subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 3 | 3 / 22 (13.64%) 6 | |
| Pancreatitis chronic | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Hepatobiliary disorders Hepatitis toxic subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Erythema subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 2 | |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Rash subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Renal and urinary disorders Calculus urinary subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Haematuria subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) | |
| occurrences (all) | 1 | 1 | |
| Arthritis reactive | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 22 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 22 (9.09%) | |
| occurrences (all) | 1 | 3 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 2 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 1 | |
| Osteochondrosis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) | |
| occurrences (all) | 0 | 2 | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bronchitis | | | |

| | | |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Conjunctivitis | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 |
| Cystitis | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 22 (4.55%) |
| occurrences (all) | 2 | 1 |
| Ear infection | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 |
| Folliculitis | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gastrointestinal infection | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Herpes virus infection | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 |
| Herpes zoster | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 22 (0.00%) |
| occurrences (all) | 2 | 0 |
| Influenza | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 1 |
| Laryngitis viral | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Nasopharyngitis | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 2 / 22 (9.09%) |
| occurrences (all) | 4 | 2 |
| Oral candidiasis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Oral herpes | | |

| | | |
|-----------------------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 22 (4.55%) |
| occurrences (all) | 3 | 1 |
| Oropharyngeal candidiasis | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pneumonia | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 22 (9.09%) |
| occurrences (all) | 1 | 4 |
| Respiratory tract infection | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Respiratory tract infection viral | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 2 / 22 (9.09%) |
| occurrences (all) | 4 | 5 |
| Rhinitis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Skin candida | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 |
| Systemic infection | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Tonsillitis | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 22 (0.00%) |
| occurrences (all) | 2 | 0 |
| Tooth infection | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 |
| Tracheobronchitis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 2 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 1 / 22 (4.55%) |
| occurrences (all) | 7 | 1 |
| Urinary tract infection | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 1 / 22 (4.55%) 1 | |
| Viral pharyngitis subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Dyslipidaemia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 22 (4.55%) 1 | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 22 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 23 April 2015 | The purpose of this amendment was to incorporate a second screening visit (Visit 2) to allow safety laboratory results to be available prior to randomization at Day 1. Moreover, some inclusion/exclusion criteria were modified, in consultation with the investigators, to simplify recruitment. |
| 29 July 2015 | The purpose of this amendment was to incorporate requests following Health Authority and Ethic Committee review. Suggestions following investigators feedback were also implemented. Given the limited clinical safety data available to date, an independent DMC was instituted to routinely monitor the safety data as requested after Health Authority Review. The manual randomization process was replaced by using a validated Interactive response technology system for patient randomization. |
| 19 May 2016 | The purpose of this amendment was to make the optional autoantibodies (anti-AChR and anti-MuSK) diagnostic test at screening visit mandatory for all patients as an inclusion criterion to confirm eligibility. This assessment was already foreseen at screening, only in case of absence of AChR or MuSK autoantibodies with a positive medical history of MG. To allow consistency in all patients for AChR or MuSK autoantibodies assessment and a positive diagnosis of MG, the assessment was made mandatory at visit 1. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported