



Clinical trial results:

Investigator- and subject-blinded, randomized, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and efficacy trial of CFZ533 in pediatric and young adult subjects with new onset type 1 diabetes (T1DM)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-004553-25 |
| Trial protocol | BE SI DE IT |
| Global end of trial date | 04 June 2024 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 02 February 2025 |
| First version publication date | 18 December 2024 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CCFZ533X2207 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04129528 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharmaceuticals |
| Sponsor organisation address | Novartis Campus, 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? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 June 2024 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 04 June 2024 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary objectives:

- To evaluate effects of CFZ533 on pancreatic beta cell function in subjects with new-onset Type 1 Diabetes Mellitus (T1DM).
- To evaluate the safety and tolerability of CFZ533 in subjects with new onset T1DM.

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 | 08 November 2019 |
| 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 | Belgium: 13 |
| Country: Number of subjects enrolled | Spain: 21 |
| Country: Number of subjects enrolled | Slovenia: 1 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Worldwide total number of subjects | 44 |
| EEA total number of subjects | 42 |

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) | 35 |
| Adults (18-64 years) | 9 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in 12 investigative sites in 6 countries.

Pre-assignment

Screening details:

Enrolment was based on both screening and baseline results. The screening and baseline visit(s) may be conducted over 1 or more visits depending on the subject's body weight and World Health Organization and European Medicines Agency (EMA) recommendations for trial related phlebotomy limits.

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, Carer, Assessor |

Arms

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

Arm description:

CFZ533 30 mg/kg i.v. dose on Day 1. From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg received 195 mg s.c., and participants with body weight of ≥ 50 kg to ≤ 125 kg received 300 mg s.c. on a weekly basis.

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

Dosage and administration details:

CFZ533 30 mg/kg i.v. dose on Day 1.

| | |
|--|--|
| Investigational medicinal product name | CFZ533 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

CFZ533 From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg received 195 mg s.c., and participants with body weight of ≥ 50 kg to ≤ 125 kg received 300 mg s.c. on a weekly basis.

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

Arm description:

Placebo i.v. dose on Day 1. From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg and body weight of ≥ 50 kg to ≤ 125 kg received matching placebo s.c. on a weekly basis.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | CFZ533 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg and body weight of ≥ 50 kg to ≤ 125 kg received matching placebo s.c. on a weekly basis.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | CFZ533 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo i.v. dose on Day 1.

| Number of subjects in period 1 | CFZ533 | Placebo |
|---------------------------------------|--------|---------|
| Started | 29 | 15 |
| Completed | 26 | 13 |
| Not completed | 3 | 2 |
| Consent withdrawn by subject | 1 | 1 |
| Physician decision | 1 | 1 |
| Adverse event | 1 | - |

Baseline characteristics

Reporting groups

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

Reporting group description:

CFZ533 30 mg/kg i.v. dose on Day 1. From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg received 195 mg s.c., and participants with body weight of ≥ 50 kg to ≤ 125 kg received 300 mg s.c. on a weekly basis.

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

Reporting group description:

Placebo i.v. dose on Day 1. From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg and body weight of ≥ 50 kg to ≤ 125 kg received matching placebo s.c. on a weekly basis.

| Reporting group values | CFZ533 | Placebo | Total |
|--|------------|------------|-------|
| Number of subjects | 29 | 15 | 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) | 23 | 12 | 35 |
| Adults (18-64 years) | 6 | 3 | 9 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 15.6 | 15.5 | |
| standard deviation | ± 2.81 | ± 3.07 | - |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 10 | 5 | 15 |
| Male | 19 | 10 | 29 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 29 | 15 | 44 |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | CFZ533 |
| Reporting group description: CFZ533 30 mg/kg i.v. dose on Day 1. From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg received 195 mg s.c., and participants with body weight of ≥ 50 kg to ≤ 125 kg received 300 mg s.c. on a weekly basis. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo i.v. dose on Day 1. From Day 8 up to Day 358 participants with body weight of ≥ 30 to < 50 kg and body weight of ≥ 50 kg to ≤ 125 kg received matching placebo s.c. on a weekly basis. | |

Primary: Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs) during the on-treatment period

| | |
|--|---|
| End point title | Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs) during the on-treatment period ^[1] |
| End point description: Number of participants with treatment emergent AEs (any AE regardless of seriousness), AEs led to study treatment discontinuation, and SAEs. On-treatment period is defined as from date of first administration of study treatment to 98 days after date of last administration of study treatment (including start and stop date). | |
| End point type | Primary |
| End point timeframe: Adverse events were reported from first dose of study treatment to 98 days after last dose, up to a maximum duration of approximately 65 weeks | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: only analyzed descriptively. | |

| End point values | CFZ533 | Placebo | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: participants | | | | |
| Adverse Events | 28 | 13 | | |
| Serious Adverse Events | 4 | 1 | | |
| AEs leading to discontinuation of study treatment | 4 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Normalized stimulated C-peptide area under the curve (AUC) at Week 52

| | |
|-----------------|---|
| End point title | Normalized stimulated C-peptide area under the curve (AUC) at Week 52 |
|-----------------|---|

End point description:

The mixed meal tolerance test (MMTT) has appropriate sensitivity to detect residual insulin secretion and beta cell function. In the MMTT, following an 8-10 hour overnight fast, a weight-based liquid meal provided as 6 mL/kg (maximum 360 mL) of mixed meal, ingested over 5 min with timed blood samples for glucose and C peptide determination obtained 10 min prior to ingestion (t = -10), at baseline (t = 0), and at 15, 30, 60, 90, and 120 min after consumption of the liquid meal. The time collections for post load samples are based on the start time of the mixed meal.

Stimulated C-peptide AUC by the standard MMTT, normalized by the duration of measurements, was analyzed with a mixed model repeated measures analysis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At Week 52, 10 min prior to ingestion, at start of ingestion, and at 15, 30, 60, 90, and 120 min after consumption of the liquid meal.

| End point values | CFZ533 | Placebo | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: nmol/L | | | | |
| geometric mean (confidence interval 80%) | 0.42 (0.36 to 0.49) | 0.36 (0.30 to 0.44) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Normalized stimulated C-peptide AUC |
| Comparison groups | CFZ533 v Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1817 ^[2] |
| Method | Mixed model repeated measure analysis |
| Parameter estimate | Ratio of geometric means CFZ533/placebo |
| Point estimate | 1.173 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.47 |

Notes:

[2] - one-sided P-value

Secondary: Maximum plasma concentration (Cmax) of CFZ533 after intravenous (IV) administration

| | |
|-----------------|--|
| End point title | Maximum plasma concentration (Cmax) of CFZ533 after intravenous (IV) administration ^[3] |
|-----------------|--|

End point description:

Cmax is defined as the maximum (peak) observed concentration following a dose. Free CFZ533 plasma concentrations were determined using a validated target-based sandwich enzyme-linked immunosorbent assay (ELISA) method.

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

End point timeframe:

Day 1: Pre-dose and 90 minutes after the start of the IV infusion (duration of the infusion is 30 minutes).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Endpoint not analyzed for participants on placebo

| End point values | CFZ533 | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | 506 (± 124) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Trough plasma concentration (C_{trough}) of CFZ533

| | |
|-----------------|---|
| End point title | Trough plasma concentration (C _{trough}) of CFZ533 ^[4] |
|-----------------|---|

End point description:

C_{trough} is the observed plasma concentration that is just prior to the beginning of, or at the end of a dosing interval. Free CFZ533 plasma concentrations were determined using a validated target-based sandwich ELISA method. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

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

End point timeframe:

Pre-dose at: Day 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK Endpoint not analyzed for participants on placebo

| End point values | CFZ533 | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: ug/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n=27) | 0.00 (± 0.00) | | | |
| Week 4 (n=26) | 182 (± 40.9) | | | |
| Week 8 (n=25) | 171 (± 45.8) | | | |
| Week 12 (n=21) | 169 (± 43.1) | | | |
| Week 16 (n=18) | 193 (± 55.2) | | | |
| Week 20 (n=20) | 184 (± 68.1) | | | |
| Week 24 (n=16) | 176 (± 65.2) | | | |
| Week 28 (n=18) | 186 (± 61.4) | | | |
| Week 32 (n=16) | 177 (± 65.4) | | | |
| Week 36 (n=17) | 180 (± 86.7) | | | |
| Week 40 (n=15) | 183 (± 80.0) | | | |
| Week 44 (n=14) | 170 (± 88.7) | | | |

| | | | | |
|----------------|-----------------|--|--|--|
| Week 48 (n=15) | 205 (± 101) | | | |
| Week 52 (n=29) | 155 (± 111) | | | |
| Week 56 (n=26) | 72.6 (± 53.3) | | | |
| Week 60 (n=25) | 30.9 (± 24.9) | | | |
| Week 64 (n=26) | 9.23 (± 11.7) | | | |
| Week 68 (n=25) | 1.86 (± 3.15) | | | |
| Week 72 (n=26) | 0.221 (± 0.499) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum plasma concentration (Tmax) of CFZ533 after IV administration

| | |
|-----------------|--|
| End point title | Time to reach maximum plasma concentration (Tmax) of CFZ533 after IV administration ^[5] |
|-----------------|--|

End point description:

Tmax is the time to reach maximum (peak) drug concentration after single-dose administration (time). Free CFZ533 plasma concentrations were determined using a validated target-based sandwich ELISA method. Theoretical sampling time points were used to report Tmax.

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

End point timeframe:

Day 1: Pre-dose and 90 minutes after the start of the IV infusion (duration of the infusion is 30 minutes).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK Endpoint not analyzed for participants on placebo

| | | | | |
|-------------------------------|------------------|--|--|--|
| End point values | CFZ533 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 29 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 1.5 (1.5 to 1.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with full or partial remission

| | |
|-----------------|---|
| End point title | Number of participants with full or partial remission |
|-----------------|---|

End point description:

Full remission is defined by HbA1c ≤ 6.5% (48 mmol/mol) and no exogenous insulin use at Week 52. Partial remission 1 is defined by Insulin Dose Adjusted HbA1c (IDAA1c) ≤ 9.0 at Week 52.

Partial remission 2 is defined by HbA1c < 7.0% (53 mmol/mol) and total daily insulin dose <0.5 units per kg per day at Week 52.

Two different criteria for partial remission were considered, and patients were assessed separately according to each criterion.

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

End point timeframe:

Week 52

| End point values | CFZ533 | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: participants | | | | |
| Full remission | 0 | 0 | | |
| Partial remission 1 | 20 | 10 | | |
| Partial remission 2 | 15 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Normalized stimulated C-peptide area under the curve (AUC) at Week 72

| | |
|-----------------|---|
| End point title | Normalized stimulated C-peptide area under the curve (AUC) at Week 72 |
|-----------------|---|

End point description:

The mixed meal tolerance test (MMTT) has appropriate sensitivity to detect residual insulin secretion and beta cell function. In the MMTT, following an 8-10 hour overnight fast, a weight-based liquid meal provided as 6 mL/kg (maximum 360 mL) of mixed meal, ingested over 5 min with timed blood samples for glucose and C peptide determination obtained 10 min prior to ingestion ($t = -10$), at baseline ($t = 0$), and at 15, 30, 60, 90, and 120 min after consumption of the liquid meal. The time collections for post load samples are based on the start time of the mixed meal.

Stimulated C-peptide AUC by the standard MMTT, normalized by the duration of measurements, was analyzed with a mixed model repeated measures analysis.

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

End point timeframe:

At Week 72, 10 min prior to ingestion, at start of ingestion, and at 15, 30, 60, 90, and 120 min after consumption of the liquid meal.

| End point values | CFZ533 | Placebo | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 15 | | |
| Units: nmol/L | | | | |
| geometric mean (confidence interval 80%) | 0.40 (0.34 to 0.47) | 0.32 (0.26 to 0.39) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus follow up period, up to a maximum duration of approximately 72 weeks.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:
CFZ533

| | |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:
Total

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

Reporting group description:
Placebo

| Serious adverse events | CFZ533 | Total | Placebo |
|--|-----------------|-----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 7 / 44 (15.91%) | 1 / 15 (6.67%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Traumatic fracture | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Tonic clonic movements | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Large intestine infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mastoiditis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 44 (2.27%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | CFZ533 | Total | Placebo |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 29 (93.10%) | 41 / 44 (93.18%) | 14 / 15 (93.33%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Medical device pain | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 8 / 44 (18.18%) | 3 / 15 (20.00%) |
| occurrences (all) | 6 | 10 | 4 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 2 | 3 | 1 |
| Injection site reaction | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 10 / 44 (22.73%) | 3 / 15 (20.00%) |
| occurrences (all) | 39 | 114 | 75 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 2 | 1 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Productive cough | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Oropharyngeal pain | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 29 (10.34%) | 4 / 44 (9.09%) | 1 / 15 (6.67%) |
| occurrences (all) | 4 | 5 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Cough | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 5 / 44 (11.36%) | 4 / 15 (26.67%) |
| occurrences (all) | 4 | 8 | 4 |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Asthma | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 44 (4.55%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 5 | 5 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 3 / 44 (6.82%) | 2 / 15 (13.33%) |
| occurrences (all) | 1 | 3 | 2 |
| Lipids increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 2 | 1 |
| SARS-CoV-2 test positive | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Serology positive | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Urine analysis abnormal | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Injury, poisoning and procedural complications | | | |
| Injection related reaction | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 2 | 8 | 6 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 2 | 1 |
| Muscle strain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Congenital, familial and genetic disorders | | | |
| Gilbert's syndrome | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 44 (4.55%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 29 (24.14%) | 9 / 44 (20.45%) | 2 / 15 (13.33%) |
| occurrences (all) | 14 | 16 | 2 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 4 / 44 (9.09%) | 0 / 15 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 2 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 6 / 44 (13.64%) | 1 / 15 (6.67%) |
| occurrences (all) | 6 | 7 | 1 |
| Abdominal pain upper | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 4 / 44 (9.09%) 4 | 2 / 15 (13.33%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 3 / 44 (6.82%) 3 | 0 / 15 (0.00%) 0 |
| Odynophagia subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 2 / 44 (4.55%) 4 | 1 / 15 (6.67%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 44 (4.55%) 2 | 0 / 15 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 9 | 4 / 44 (9.09%) 9 | 0 / 15 (0.00%) 0 |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Dermatitis atopic subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 2 | 1 / 15 (6.67%) 2 |
| Acne subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 44 (4.55%) 2 | 0 / 15 (0.00%) 0 |
| Ingrowing nail subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 44 (4.55%) 2 | 0 / 15 (0.00%) 0 |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|------------------------|------------------------|----------------------|
| Back pain subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 44 (4.55%) 2 | 0 / 15 (0.00%) 0 |
| Infections and infestations | | | |
| COVID-19 subjects affected / exposed occurrences (all) | 7 / 29 (24.14%) 7 | 9 / 44 (20.45%) 9 | 2 / 15 (13.33%) 2 |
| Chronic active Epstein-Barr virus infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Cytomegalovirus infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Epstein-Barr virus infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 5 / 44 (11.36%) 8 | 2 / 15 (13.33%) 5 |
| Gastroenteritis viral subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Influenza subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 4 | 6 / 44 (13.64%) 7 | 3 / 15 (20.00%) 3 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 13 / 29 (44.83%) 33 | 18 / 44 (40.91%) 42 | 5 / 15 (33.33%) 9 |
| Otitis externa subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 2 | 2 / 44 (4.55%) 3 | 1 / 15 (6.67%) 1 |
| Parvovirus B19 infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 44 (2.27%) 1 | 1 / 15 (6.67%) 1 |
| Pharyngitis | | | |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 3 | 2 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 44 (4.55%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 3 / 44 (6.82%) | 0 / 15 (0.00%) |
| occurrences (all) | 7 | 7 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 4 / 44 (9.09%) | 2 / 15 (13.33%) |
| occurrences (all) | 2 | 5 | 3 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 44 (2.27%) | 1 / 15 (6.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Tinea pedis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 3 / 44 (6.82%) | 3 / 15 (20.00%) |
| occurrences (all) | 0 | 4 | 4 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 44 (4.55%) | 2 / 15 (13.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 7 / 44 (15.91%) | 3 / 15 (20.00%) |
| occurrences (all) | 9 | 12 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 44 (4.55%) | 0 / 15 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 44 (4.55%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 2 | 1 |

| | | | |
|---|-------------------------|-------------------------|------------------------|
| Hypoglycaemia subjects affected / exposed occurrences (all) | 19 / 29 (65.52%) 181 | 27 / 44 (61.36%) 285 | 8 / 15 (53.33%) 104 |
|---|-------------------------|-------------------------|------------------------|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 25 July 2019 | This protocol amendment addresses comments received from Federal Agency for Medicines and Health Products in the letter dated 08July2019. |
| 10 December 2019 | The purpose of this amendment was to include additional safety monitoring that has already been implemented via urgent safety measures (USMs) in response to a suspected unexpected serious adverse reaction that was reported in another CFZ533 study of lupus nephritis patients. |
| 30 November 2020 | The purpose of this amendment was to include additional safety monitoring in response to the newly prevalent community exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). |
| 04 January 2021 | Based on comments by the MHRA, the age classifications in the Cohorts have been revised to be more in line with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Topic E11 age classifications. |
| 17 March 2022 | The purpose of this amendment was to implement a Hybrid Trial Design which included a flexible model for incorporating both on-site (traditional on-site based) and off-site (also known as remote or decentralized) elements within the same study design. |
| 03 April 2023 | The purpose of this protocol amendment was primarily to reduce the sample size and duration of study conduct. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|---|----------------|
| 16 March 2020 | There was a temporary halt implemented for both recruitment and treatment of participants on 16-Mar-2020 due to the COVID-19 worldwide pandemic with the trial approved to restart on 27-Aug-2020 based on country and site feasibility coming out of COVID-19. | 27 August 2020 |

Notes:

Limitations and caveats

None reported