



Clinical trial results: Effect of calcium dobesilate in early stages of diabetic retinopathy Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-000250-19 |
| Trial protocol | ES |
| Global end of trial date | 24 November 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 09 June 2022 |
| First version publication date | 09 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CADODIAME |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | VHIR |
| Sponsor organisation address | Passeig Vall Hebron 119-129, Barcelona, Spain, 08035 |
| Public contact | Joaquin Lopez-Soriano, Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), 34 934894172, joaquin.lopez.soriano@vhir.org |
| Scientific contact | Rafael Simó, Fundació Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), 34 934894172, rafael.simo@vhir.org |

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 | 24 November 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 November 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 November 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine whether Doxium® is able to prevent or reduce thickening of the retina.

Protection of trial subjects:

Treatment was interrupted if any contraindication was observed, or if laboratory analyses were abnormal, according to clinicians criterion. No other measures were required for the treatment

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 09 October 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 60 |
| Worldwide total number of subjects | 60 |
| EEA total number of subjects | 60 |

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) | 30 |
| From 65 to 84 years | 30 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

235 patients were recruited in 3 hospitals from Catalonia

Pre-assignment

Screening details:

65 patients met the requirements. Finally, 61 were selected, and 60 engaged in the study. Inclusion criteria were Type2 diabetes, subclinical macular edema, ETDRS 20-47, diabetes diagnosed for more than 5 years, 49-75 years of age, HbA1c $\geq 6.5\%$ and $\leq 9.5\%$ at 6 months previous to the screening

Period 1

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

Arms

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

Arm description: -

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Calcium dobesilate |
| Investigational medicinal product code | |
| Other name | Doxium |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 tablets in the morning (2x500 mg) and 2 at night (2x500 mg), orally (total daily dose: 2000 mg)

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

Arm description: -

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Lactose |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral daily, same conditions as treatment

| Number of subjects in period 1 | Dobesilate | Placebo |
|--------------------------------|------------|---------|
| Started | 30 | 30 |
| Completed | 29 | 22 |
| Not completed | 1 | 8 |
| Adverse event, non-fatal | 1 | 8 |

Baseline characteristics

Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 60 | 60 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 65.43 | | |
| full range (min-max) | 49 to 80 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 22 | 22 | |
| Male | 38 | 38 | |

End points

End points reporting groups

| | |
|--------------------------------|------------|
| Reporting group title | Dobesilate |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

Primary: Retinal thickness

| | |
|------------------------|---|
| End point title | Retinal thickness |
| End point description: | Difference in retinal thickness from initial visit to 12 months visit, assessed by SD-OCT |
| End point type | Primary |
| End point timeframe: | 12 months |

| End point values | Dobesilate | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 24 | | |
| Units: micrometer(s) | | | | |
| arithmetic mean (standard deviation) | 1 (\pm 24) | 4 (\pm 24) | | |

Statistical analyses

| | |
|---|----------------------|
| Statistical analysis title | Retinal thickness |
| Comparison groups | Placebo v Dobesilate |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.7092 |
| Method | t-test, 2-sided |

Secondary: Visual acuity

| | |
|------------------------|---------------|
| End point title | Visual acuity |
| End point description: | ETDRS scale |
| End point type | Secondary |
| End point timeframe: | 12 months |

| End point values | Dobesilate | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 24 | | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 0) | 0 (\pm 0) | | |

Statistical analyses

| Statistical analysis title | Visual acuity |
|---|----------------------|
| Comparison groups | Dobesilate v Placebo |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.9783 |
| Method | t-test, 2-sided |

Secondary: Change in EDTRS

| | |
|------------------------|-----------------|
| End point title | Change in EDTRS |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Dobesilate | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 30 | | |
| Units: subjects | 25 | 24 | | |

Statistical analyses

| Statistical analysis title | EDTRS |
|----------------------------|----------------------|
| Comparison groups | Dobesilate v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.1706 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Retinal volume

| | |
|------------------------|----------------|
| End point title | Retinal volume |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Dobesilate | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 24 | | |
| Units: cubic millimeters | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 0) | 0 (\pm 0) | | |

Statistical analyses

| | |
|---|----------------------|
| Statistical analysis title | Retinal volume |
| Comparison groups | Dobesilate v Placebo |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.6366 |
| Method | t-test, 2-sided |

Secondary: Ganglionar layer

| | |
|--|------------------|
| End point title | Ganglionar layer |
| End point description: | |
| Difference in ganglionar layer thickness between 12 months and first visit | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Dobesilate | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 24 | | |
| Units: micrometer(s) | | | | |
| arithmetic mean (standard deviation) | -3 (\pm 21) | -2 (\pm 13) | | |

Statistical analyses

| Statistical analysis title | Ganglionar layer |
|---|----------------------|
| Comparison groups | Dobesilate v Placebo |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.7603 |
| Method | t-test, 2-sided |

Secondary: Nervous fiber layer

| | |
|------------------------|---------------------|
| End point title | Nervous fiber layer |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Dobesilate | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 18 | | |
| Units: micrometer(s) | | | | |
| arithmetic mean (standard deviation) | 0 (\pm 2) | 2 (\pm 8) | | |

Statistical analyses

| Statistical analysis title | Nervous fiber layer |
|---|----------------------|
| Comparison groups | Dobesilate v Placebo |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.33 |
| Method | t-test, 2-sided |

Secondary: Foveal area

| | |
|-----------------|-------------|
| End point title | Foveal area |
|-----------------|-------------|

End point description:

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

End point timeframe:

12 months

| End point values | Dobesilate | Placebo | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 21 | | |
| Units: square millimeter | | | | |
| arithmetic mean (standard error) | 0 (± 2) | 0 (± 0) | | |

Statistical analyses

| Statistical analysis title | Foveolar area |
|---|----------------------|
| Comparison groups | Dobesilate v Placebo |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.2898 |
| Method | t-test, 2-sided |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 24 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Dobesilate |
|-----------------------|------------|

Reporting group description: -

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

Reporting group description: -

| Serious adverse events | Dobesilate | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 30 (20.00%) | 4 / 30 (13.33%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Aspiration pleural cavity | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Penile discomfort | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Dobesilate | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 30 (90.00%) | 25 / 30 (83.33%) | |

| | | | |
|---|----------------|----------------|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cutaneous T-cell lymphoma | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lipoma | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Surgical and medical procedures | | | |
| Gastric polypectomy | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tumour excision | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|--|---------------------|---------------------|--|
| Breast capsulotomy subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Polypectomy subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Tooth extraction subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Lens capsulotomy subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| General disorders and administration site conditions | | | |
| Pain subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 2 / 30 (6.67%) 2 | |
| Swelling subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Condition aggravated subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 2 / 30 (6.67%) 2 | |
| Gait disturbance subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Chest discomfort subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Polyp | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 30 (13.33%) | 4 / 30 (13.33%) | |
| occurrences (all) | 4 | 4 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Hiccups | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pleural disorder | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Orthopnoea | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngeal oedema | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Dysphonia subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Psychiatric disorders Restlessness subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Depression subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Investigations Weight loss subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Injury, poisoning and procedural complications Cystitis subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Fracture subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Wound subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Contusion subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 1 / 30 (3.33%) 1 | |
| Arthropod bite subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Cardiac disorders | | | |

| | | | |
|-------------------------------------|----------------|----------------|--|
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tachycardia paroxysmal | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertensive cardiomyopathy | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Nerve compression | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular headache | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diabetic neuropathy | | | |

| | | | |
|-------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Radiculopathy | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Carotid artery thrombosis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Optic neuritis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| Tympanic membrane perforation | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Iridocyclitis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Macular oedema | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 2 / 30 (6.67%) | |
| occurrences (all) | 1 | 2 | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye inflammation | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 1 / 30 (3.33%) 1 | |
| Gastrointestinal disorders | | | |
| Gastric erosive | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anal incontinence | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Odynophagia | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip pain | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---------------------|---------------------|--|
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Hepatobiliary disorders Hepatic mass subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Liver disorder subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 1 / 30 (3.33%) 1 | |
| Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 1 / 30 (3.33%) 1 | |
| Intertrigo subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Erythema subjects affected / exposed occurrences (all) | 2 / 30 (6.67%) 2 | 0 / 30 (0.00%) 0 | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Dermatitis contact subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Lipodystrophy acquired subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Renal and urinary disorders Diabetic nephropathy subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 30 (0.00%) 0 | |
| Albuminuria | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bladder spasm | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Microalbuminuria | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Endocrine disorders | | | |
| Adrenal atrophy | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Nasopharyngitis | | | |

| | | | |
|------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 2 / 30 (6.67%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 2 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Syphilis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Renal cyst infection | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 3 / 30 (10.00%) | |
| occurrences (all) | 1 | 3 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|-----------------------------|----------------|----------------|--|
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported