



Clinical trial results:

A 24 Week, Phase IIa, Double blind, Randomized, Parallel Group, Placebo-controlled, Proof of Concept Study to Assess the Efficacy and Safety of Two Doses of 5 Aminolevulinic Acid Co-administered with Sodium Ferrous Citrate in Adult Patients with Type 2 Diabetes Mellitus Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-004944-39 |
| Trial protocol | EE HU PL RO |
| Global end of trial date | 17 February 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 04 December 2021 |
| First version publication date | 04 December 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | NPJ005-DM2-0522 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | neopharma Japan |
| Sponsor organisation address | 2nd Floor, PMO Kojimachi, Kojimachi 6-2-6, Chiyoda-ku, Tokyo, Japan, 102-0083 |
| Public contact | Clinical Trial Information Desk, neopharma Japan Co., Ltd., npjprd@neopharmajp.com |
| Scientific contact | Clinical Trial Information Desk, neopharma Japan Co., Ltd., npjprd@neopharmajp.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 | 16 February 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 February 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 February 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the change from Baseline in Glycated hemoglobin (HbA1c) up to Week 24 between each dose combination of 5 aminolevulinic acid/sodium ferrous citrate (5 ALA/SFC) and placebo.

Protection of trial subjects:

Patients were enrolled in the study only after providing informed consent, and undergoing inclusion and exclusion assessments.

Rescue therapy for patients in either treatment arm with prandial insulin or oral antidiabetic (OAD) therapy was offered per Investigator's discretion and in consultation with Medical Monitor from randomization until end of the study, depending on fasting blood glucose values.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 09 April 2018 |
| 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 | Poland: 43 |
| Country: Number of subjects enrolled | Estonia: 42 |
| Country: Number of subjects enrolled | Hungary: 41 |
| Country: Number of subjects enrolled | Romania: 46 |
| Country: Number of subjects enrolled | Ukraine: 46 |
| Worldwide total number of subjects | 218 |
| EEA total number of subjects | 172 |

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) | 130 |
| From 65 to 84 years | 88 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

218 patients were enrolled at 74 sites in Hungary, Poland, Estonia, Romania and Ukraine from 31-May-2018 to 17-Feb-2020.

Pre-assignment

Screening details:

434 potential patients underwent a screening period of maximally 2 weeks. Eligible patients enrolled with current OAD monotherapy underwent a 4-week Washout period followed by a 2-week single-blinded Placebo run-in period before entering the 24-week Treatment period.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment period (24 weeks) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Carer, Subject |

Blinding implementation details:

The appearance, including packaging and labeling of the study treatment (capsules, packaging) was the same for 5-ALA/SFC and the placebo.

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 5-ALA-HCl 150 mg/SFC 118 mg |

Arm description:

The patients received 5-ALA/SFC at a dose of 150 mg/118 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg for 24 weeks.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | 5-aminolevulinic acid hydrochloride/sodium ferrous citrate (5-ALA-HCl/SFC) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

5-ALA/SFC was administered orally at a dose of 150 mg/119 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg at least 8 hours apart in the morning and evening, after the meal, for 24 weeks.

| | |
|------------------|---------------------------|
| Arm title | 5-ALA-HCl 50 mg/SFC 39 mg |
|------------------|---------------------------|

Arm description:

The patients received 5-ALA/SFC at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg for 24 weeks.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | 5-aminolevulinic acid hydrochloride/sodium ferrous citrate (5-ALA-HCl/SFC) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

5-ALA/SFC was administered orally at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg at least 8 hours apart in the morning and evening, after the meal, for 24 weeks.

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

Arm description:

The patients received an equal number of matching placebo capsules (BID) for 24 weeks.

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

Dosage and administration details:

Matching placebo capsules were administered in the same manner as the test product.

| Number of subjects in period 1 | 5-ALA-HCl 150 mg/SFC 118 mg | 5-ALA-HCl 50 mg/SFC 39 mg | Placebo |
|---------------------------------------|------------------------------------|----------------------------------|----------------|
| Started | 72 | 73 | 73 |
| Completed | 63 | 56 | 60 |
| Not completed | 9 | 17 | 13 |
| Consent withdrawn by subject | 2 | 4 | 3 |
| Adverse event, non-fatal | 2 | 4 | 2 |
| Other | - | - | 1 |
| Rescue Criteria Met | 4 | 8 | 6 |
| Use of Prohibited Medication | 1 | 1 | - |
| Noncompliance with protocol | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|-----------------------------|
| Reporting group title | 5-ALA-HCl 150 mg/SFC 118 mg |
| Reporting group description: The patients received 5-ALA/SFC at a dose of 150 mg/118 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg for 24 weeks. | |
| Reporting group title | 5-ALA-HCl 50 mg/SFC 39 mg |
| Reporting group description: The patients received 5-ALA/SFC at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg for 24 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: The patients received an equal number of matching placebo capsules (BID) for 24 weeks. | |

| Reporting group values | 5-ALA-HCl 150 mg/SFC 118 mg | 5-ALA-HCl 50 mg/SFC 39 mg | Placebo |
|---|-----------------------------|---------------------------|---------|
| Number of subjects | 72 | 73 | 73 |
| Age categorical Units: Subjects | | | |
| < 65 years | 42 | 43 | 45 |
| ≥ 65 years | 30 | 30 | 28 |
| Age continuous Units: years | | | |
| arithmetic mean | 60.2 | 61.6 | 59.4 |
| standard deviation | ± 9.48 | ± 8.16 | ± 9.53 |
| Gender categorical Units: Subjects | | | |
| Female | 41 | 39 | 40 |
| Male | 31 | 34 | 33 |
| Ethnicity Units: Subjects | | | |
| Not Hispanic or Latino | 72 | 73 | 73 |
| Race Units: Subjects | | | |
| White | 72 | 73 | 73 |
| Oral antidiabetic mono therapy Units: Subjects | | | |
| Yes | 45 | 46 | 46 |
| No | 27 | 27 | 27 |
| Treatment-Free Status Units: Subjects | | | |
| Yes | 27 | 27 | 27 |
| No | 45 | 46 | 46 |
| Complication related T2DM Units: Subjects | | | |
| Yes | 8 | 8 | 7 |
| No | 64 | 65 | 66 |
| HbA1c Units: Subjects | | | |

| | | | |
|------|----|----|----|
| < 8% | 55 | 57 | 54 |
| ≥ 8% | 17 | 16 | 19 |

| | | | |
|--|-------------------|-------------------|-------------------|
| Height Units: cm arithmetic mean standard deviation | 167.17 ± 9.264 | 168.46 ± 8.947 | 168.67 ± 9.293 |
| Weight Units: kg arithmetic mean standard deviation | 91.74 ± 14.894 | 91.50 ± 16.602 | 94.07 ± 15.477 |
| BMI Units: kg/m2 arithmetic mean standard deviation | 32.76 ± 4.102 | 32.10 ± 4.283 | 32.96 ± 4.057 |
| Waist Circumference Units: cm arithmetic mean standard deviation | 107.7 ± 13.04 | 107.6 ± 12.85 | 108.4 ± 11.61 |
| Systolic blood pressure Units: mmHg arithmetic mean standard deviation | 133.0 ± 10.32 | 131.8 ± 13.47 | 133.7 ± 11.22 |
| Diastolic blood pressure Units: mmHg arithmetic mean standard deviation | 78.0 ± 7.01 | 78.3 ± 8.42 | 79.2 ± 7.89 |
| HbA1c Units: percent arithmetic mean standard deviation | 7.34 ± 0.698 | 7.37 ± 0.875 | 7.49 ± 0.757 |
| Duration of T2DM Units: years arithmetic mean standard deviation | 4.94 ± 4.695 | 6.21 ± 5.051 | 6.83 ± 5.717 |
| Fasting C-peptide Units: nmol/L arithmetic mean standard deviation | 1.045 ± 0.5062 | 0.968 ± 0.4234 | 0.920 ± 0.3573 |
| Fasting Plasma Glucose Units: mmol/L arithmetic mean standard deviation | 8.70 ± 1.996 | 8.90 ± 2.200 | 9.18 ± 1.989 |
| eGFR Units: ml/min/1.73m2 arithmetic mean standard deviation | 94.71 ± 22.552 | 91.87 ± 20.969 | 94.21 ± 20.061 |
| Serum Zinc | | | |
| The threshold of serum zinc ≥ lower level was 9.2 µmol/L (range: 9.2 to 19.9 µmol/L) | | | |
| Units: µg/dL arithmetic mean | 15.29 | 14.74 | 14.10 |

| | | | |
|--------------------|---------|---------|---------|
| standard deviation | ± 3.678 | ± 4.360 | ± 2.957 |
| CGM | | | |
| Units: mg/dL | | | |
| arithmetic mean | 116.7 | 126.4 | 113.8 |
| standard deviation | ± 70.92 | ± 71.93 | ± 68.62 |

| | | | |
|--------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 218 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| < 65 years | 130 | | |
| ≥ 65 years | 88 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 120 | | |
| Male | 98 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 218 | | |
| Race | | | |
| Units: Subjects | | | |
| White | 218 | | |
| Oral antidiabetic mono therapy | | | |
| Units: Subjects | | | |
| Yes | 137 | | |
| No | 81 | | |
| Treatment-Free Status | | | |
| Units: Subjects | | | |
| Yes | 81 | | |
| No | 137 | | |
| Complication related T2DM | | | |
| Units: Subjects | | | |
| Yes | 23 | | |
| No | 195 | | |
| HbA1c | | | |
| Units: Subjects | | | |
| < 8% | 166 | | |
| ≥ 8% | 52 | | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| BMI | | | |

| | | | |
|---|---|--|--|
| Units: kg/m2 arithmetic mean standard deviation | - | | |
| Waist Circumference Units: cm arithmetic mean standard deviation | - | | |
| Systolic blood pressure Units: mmHg arithmetic mean standard deviation | - | | |
| Diastolic blood pressure Units: mmHg arithmetic mean standard deviation | - | | |
| HbA1c Units: percent arithmetic mean standard deviation | - | | |
| Duration of T2DM Units: years arithmetic mean standard deviation | - | | |
| Fasting C-peptide Units: nmol/L arithmetic mean standard deviation | - | | |
| Fasting Plasma Glucose Units: mmol/L arithmetic mean standard deviation | - | | |
| eGFR Units: ml/min/1.73m2 arithmetic mean standard deviation | - | | |
| Serum Zinc | | | |
| The threshold of serum zinc \geq lower level was 9.2 μ mol/L (range: 9.2 to 19.9 μ mol/L) | | | |
| Units: μ g/dL arithmetic mean standard deviation | - | | |
| CGM Units: mg/dL arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | 5-ALA-HCl 150 mg/SFC 118 mg |
| Reporting group description: The patients received 5-ALA/SFC at a dose of 150 mg/118 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg for 24 weeks. | |
| Reporting group title | 5-ALA-HCl 50 mg/SFC 39 mg |
| Reporting group description: The patients received 5-ALA/SFC at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg for 24 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: The patients received an equal number of matching placebo capsules (BID) for 24 weeks. | |

Primary: Change from baseline in HbA1c to Week 24

| | |
|--|--|
| End point title | Change from baseline in HbA1c to Week 24 |
| End point description: | |
| End point type | Primary |
| End point timeframe: From baseline to Week 24 | |

| End point values | 5-ALA-HCl 150 mg/SFC 118 mg | 5-ALA-HCl 50 mg/SFC 39 mg | Placebo | |
|-------------------------------------|-----------------------------|---------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 72 | 71 | 70 | |
| Units: percent | | | | |
| least squares mean (standard error) | -0.27 (± 0.076) | -0.01 (± 0.080) | 0.00 (± 0.078) | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Primary efficacy |
| Statistical analysis description: The evaluation of mean change from Baseline in HbA1c compared to Placebo will be done using the Placebo Multiple Imputation (pMI) method followed by analysis using an Analysis of Covariance (ANCOVA) model with Full Analysis Set data. | |
| Comparison groups | 5-ALA-HCl 150 mg/SFC 118 mg v 5-ALA-HCl 50 mg/SFC 39 mg v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | ANCOVA |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs (TEAEs) were defined as AEs that first occurred or worsened in severity after the first administration of the study medication, until end of the study.

Adverse event reporting additional description:

An Adverse Event was any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | 5-ALA/SFC 150 mg/118 mg |
|-----------------------|-------------------------|

Reporting group description: -

| | |
|-----------------------|-----------------------|
| Reporting group title | 5-ALA/SFC 50 mg/39 mg |
|-----------------------|-----------------------|

Reporting group description: -

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

Reporting group description: -

| Serious adverse events | 5-ALA/SFC 150 mg/118 mg | 5-ALA/SFC 50 mg/39 mg | Placebo |
|---|-------------------------|-----------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 72 (4.17%) | 2 / 73 (2.74%) | 2 / 73 (2.74%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lipoma | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 73 (1.37%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 73 (1.37%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 73 (0.00%) | 1 / 73 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Oedematous pancreatitis | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 73 (0.00%) | 1 / 73 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 73 (1.37%) | 0 / 73 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Non-serious adverse events | 5-ALA/SFC 150 mg/118 mg | 5-ALA/SFC 50 mg/39 mg | Placebo |
|---|--------------------------------|------------------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 72 (63.89%) | 48 / 73 (65.75%) | 44 / 73 (60.27%) |
| Investigations | | | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 3 / 73 (4.11%) | 0 / 73 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 0 / 73 (0.00%) | 2 / 73 (2.74%) |
| occurrences (all) | 2 | 0 | 2 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 73 (0.00%) | 2 / 73 (2.74%) |
| occurrences (all) | 1 | 0 | 2 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 2 / 73 (2.74%) | 0 / 73 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 2 / 73 (2.74%) | 4 / 73 (5.48%) |
| occurrences (all) | 2 | 2 | 4 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 73 (0.00%) | 2 / 73 (2.74%) |
| occurrences (all) | 1 | 0 | 2 |
| Headache | | | |
| subjects affected / exposed | 3 / 72 (4.17%) | 1 / 73 (1.37%) | 0 / 73 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 2 / 73 (2.74%) | 0 / 73 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Sciatica subjects affected / exposed occurrences (all) | 2 / 72 (2.78%) 2 | 0 / 73 (0.00%) 0 | 0 / 73 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 72 (4.17%) 7 | 2 / 73 (2.74%) 2 | 2 / 73 (2.74%) 2 |
| Muscle spasms subjects affected / exposed occurrences (all) | 2 / 72 (2.78%) 2 | 0 / 73 (0.00%) 0 | 0 / 73 (0.00%) 0 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 72 (1.39%) 1 | 4 / 73 (5.48%) 4 | 3 / 73 (4.11%) 3 |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 72 (2.78%) 2 | 4 / 73 (5.48%) 4 | 1 / 73 (1.37%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 72 (4.17%) 4 | 2 / 73 (2.74%) 2 | 1 / 73 (1.37%) 1 |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 72 (1.39%) 1 | 2 / 73 (2.74%) 2 | 1 / 73 (1.37%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 72 (1.39%) 1 | 1 / 73 (1.37%) 1 | 2 / 73 (2.74%) 3 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 72 (0.00%) 0 | 2 / 73 (2.74%) 2 | 2 / 73 (2.74%) 2 |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 72 (0.00%) 0 | 2 / 73 (2.74%) 2 | 0 / 73 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 72 (0.00%) 0 | 0 / 73 (0.00%) 0 | 2 / 73 (2.74%) 2 |
| Viral pharyngitis | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 72 (2.78%) 2 | 0 / 73 (0.00%) 0 | 0 / 73 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 15 / 72 (20.83%) | 17 / 73 (23.29%) | 18 / 73 (24.66%) |
| occurrences (all) | 46 | 47 | 36 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 5 / 72 (6.94%) | 1 / 73 (1.37%) | 2 / 73 (2.74%) |
| occurrences (all) | 7 | 1 | 3 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 2 / 73 (2.74%) | 0 / 73 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 0 / 73 (0.00%) | 0 / 73 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 27 March 2018 | Inclusion and exclusion criteria was amended as a result of the feedback received from VHP. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported