



Clinical trial results:

Efficacy and safety of 3 doses of S201086/GLPG1972 administered orally once daily in patients with knee osteoarthritis. A 52-week international, multi-regional, multi-centre, randomised, double-blind, placebo-controlled, dose-ranging study.

ROCCELLA Study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-004581-10 |
| Trial protocol | ES HU DK PL BG |
| Global end of trial date | 14 July 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 May 2021 |
| First version publication date | 06 May 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CL2-201086-002 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03595618 |
| WHO universal trial number (UTN) | U1111-1205-0321 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Institut de Recherches Internationales Servier |
| Sponsor organisation address | 50 rue Carnot, Suresnes, France, 92284 |
| Public contact | Neuro-ImmunoInflammation Therapeutic Area, Institut de Recherches Internationales Servier, +33 1 55 72 70 63, clinicaltrials@servier.com |
| Scientific contact | Neuro-ImmunoInflammation Therapeutic Area, Institut de Recherches Internationales Servier, +33 1 55 72 70 63, clinicaltrials@servier.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 | 14 July 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 July 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 July 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of at least one dose (among 3 doses) of S201086 compared to placebo after 52 weeks of treatment in reducing cartilage loss measured by cartilage thickness using quantitative magnetic resonance imaging (qMRI) of the central medial tibiofemoral compartment (cMTFC) of the target knee.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 14 August 2018 |
| 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 | Argentina: 67 |
| Country: Number of subjects enrolled | Brazil: 139 |
| Country: Number of subjects enrolled | Canada: 64 |
| Country: Number of subjects enrolled | Japan: 67 |
| Country: Number of subjects enrolled | Korea, Republic of: 31 |
| Country: Number of subjects enrolled | Russian Federation: 38 |
| Country: Number of subjects enrolled | Taiwan: 16 |
| Country: Number of subjects enrolled | United States: 326 |
| Country: Number of subjects enrolled | Denmark: 74 |
| Country: Number of subjects enrolled | Hungary: 32 |
| Country: Number of subjects enrolled | Poland: 52 |
| Country: Number of subjects enrolled | Spain: 26 |
| Worldwide total number of subjects | 932 |
| EEA total number of subjects | 184 |

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) | 503 |
| From 65 to 84 years | 429 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female patients aged from 40 to 75 years with history of knee pain for at least 6 months and on the majority of days (> 50%) during the preceding month, symptom severity defined by a pain \geq 40 mm and \leq 90 mm on a 100 mm VAS, diagnosed for knee OA based on clinical and radiological criteria of the American College of Rheumatology.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall treatment period (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 | S201086/GLPG1972 75mg |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | S201086/GLPG1972 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

-S201086/GLPG1972 75 mg/day: From the day of inclusion until the W052 visit, the patient had to take 4 tablets orally once a day with a glass of water preferably in the morning (at the same time), corresponding to 1 tablet of 75 mg + 3 matching tablets of placebo.

| | |
|--|------------------------|
| Arm title | S201086/GLPG1972 150mg |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | S201086/GLPG1972 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

-S201086/GLPG1972 150 mg/day: From the day of inclusion until the W052 visit, the patient had to take 4 tablets orally once a day with a glass of water preferably in the morning (at the same time), corresponding to 2 tablets of 75 mg + 2 matching tablets of placebo.

| | |
|--|------------------------|
| Arm title | S201086/GLPG1972 300mg |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | S201086/GLPG1972 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

-S201086/GLPG1972 300 mg/day: From the day of inclusion until the W052 visit, the patient had to take 4 tablets orally once a day with a glass of water preferably in the morning (at the same time), corresponding to 4 tablets of 75 mg.

| | |
|--|--------------------|
| Arm title | Placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo: From the day of inclusion until the W052 visit, the patient had to take 4 tablets orally once a day with a glass of water preferably in the morning (at the same time), corresponding to 4 matching tablets of placebo.

| Number of subjects in period 1 | S201086/GLPG1972 75mg | S201086/GLPG1972 150mg | S201086/GLPG1972 300mg |
|---------------------------------------|--------------------------|---------------------------|---------------------------|
| Started | 234 | 231 | 233 |
| Completed | 191 | 191 | 177 |
| Not completed | 43 | 40 | 56 |
| Adverse event, serious fatal | - | 1 | - |
| Consent withdrawn by subject | 12 | 14 | 14 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | 16 | 16 | 20 |
| Other | 7 | 5 | 10 |
| Lost to follow-up | 6 | 4 | 5 |
| Protocol deviation | 2 | - | 6 |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 234 |
| Completed | 200 |
| Not completed | 34 |
| Adverse event, serious fatal | - |
| Consent withdrawn by subject | 10 |
| Physician decision | 2 |
| Adverse event, non-fatal | 8 |
| Other | 6 |
| Lost to follow-up | 6 |
| Protocol deviation | 2 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|------------------------|
| Reporting group title | S201086/GLPG1972 75mg |
| Reporting group description: - | |
| Reporting group title | S201086/GLPG1972 150mg |
| Reporting group description: - | |
| Reporting group title | S201086/GLPG1972 300mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | S201086/GLPG1972 75mg | S201086/GLPG1972 150mg | S201086/GLPG1972 300mg |
|---------------------------------------|--------------------------|---------------------------|---------------------------|
| Number of subjects | 234 | 231 | 233 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 125 | 125 | 130 |
| From 65-84 years | 109 | 106 | 103 |
| Age continuous Units: years | | | |
| arithmetic mean | 62.9 | 63.2 | 62.1 |
| standard deviation | ± 7.5 | ± 7.2 | ± 7.4 |
| Gender categorical Units: Subjects | | | |
| Female | 164 | 165 | 154 |
| Male | 70 | 66 | 79 |

| Reporting group values | Placebo | Total | |
|---------------------------------------|---------|-------|--|
| Number of subjects | 234 | 932 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 123 | 503 | |
| From 65-84 years | 111 | 429 | |
| Age continuous Units: years | | | |
| arithmetic mean | 63.3 | - | |
| standard deviation | ± 7.1 | | |
| Gender categorical Units: Subjects | | | |
| Female | 163 | 646 | |
| Male | 71 | 286 | |

End points

End points reporting groups

| | |
|--------------------------------|------------------------|
| Reporting group title | S201086/GLPG1972 75mg |
| Reporting group description: - | |
| Reporting group title | S201086/GLPG1972 150mg |
| Reporting group description: - | |
| Reporting group title | S201086/GLPG1972 300mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

Primary: Change from baseline to W052 in cartilage thickness of the central medial tibiofemoral compartment of the target knee by using qMRI (mm)

| | |
|------------------------|--|
| End point title | Change from baseline to W052 in cartilage thickness of the central medial tibiofemoral compartment of the target knee by using qMRI (mm) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | The cartilage thickness was measured at baseline (before inclusion), at the W028 and W052 visits, and at the WD if the time window between WD and the previous qMRI (W000 or W028) was ≥ 2 months . |

| End point values | S201086/GLPG 1972 75mg | S201086/GLPG 1972 150mg | S201086/GLPG 1972 300mg | Placebo |
|--------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 234 ^[1] | 231 ^[2] | 233 ^[3] | 234 ^[4] |
| Units: No unit | | | | |
| arithmetic mean (standard deviation) | -0.06791 (\pm 0.20169) | -0.09693 (\pm 0.26839) | -0.08545 (\pm 0.21697) | -0.11562 (\pm 0.27275) |

Notes:

- [1] - Arithmetic mean is based on 162 patients with measured value at baseline and W52
- [2] - Arithmetic mean is based on 158 patients with measured value at baseline and W52
- [3] - Arithmetic mean is based on 151 patients with measured value at baseline and W52
- [4] - Arithmetic mean is based on 172 patients with measured value at baseline and W52

Statistical analyses

| | |
|---|--|
| Statistical analysis title | S201086/GLPG1972 75mg minus placebo |
| Comparison groups | S201086/GLPG1972 75mg v Placebo |
| Number of subjects included in analysis | 468 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.165 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.04514 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.00317 |
| upper limit | 0.09345 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02465 |

Notes:

[5] - Estimate of the adjusted difference from baseline to last post baseline value between treatment groups means: each S201086/GLPG1972 dose regimen minus placebo using a MMRM including the fixed, categorical effects of treatment, region, time and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline and time-by-baseline interaction preceded by a Multiple Imputation step for patients without post-baseline measurement.

| | |
|---|--|
| Statistical analysis title | S201086/GLPG1972 150mg minus placebo |
| Comparison groups | S201086/GLPG1972 150mg v Placebo |
| Number of subjects included in analysis | 465 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.939 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.012 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03868 |
| upper limit | 0.06267 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02585 |

Notes:

[6] - Estimate of the adjusted difference from baseline to last post baseline value between treatment groups means: each S201086/GLPG1972 dose regimen minus placebo using a MMRM including the fixed, categorical effects of treatment, region, time and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline and time-by-baseline interaction preceded by a Multiple Imputation step for patients without post-baseline measurement.

| | |
|---|--|
| Statistical analysis title | S201086/GLPG1972 300mg minus placebo |
| Comparison groups | S201086/GLPG1972 300mg v Placebo |
| Number of subjects included in analysis | 467 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.682 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | Adjusted mean difference |
| Point estimate | 0.02329 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02641 |
| upper limit | 0.073 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02536 |

Notes:

[7] - Estimate of the adjusted difference from baseline to last post baseline value between treatment groups means: each S201086/GLPG1972 dose regimen minus placebo using a MMRM including the fixed, categorical effects of treatment, region, time and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline and time-by-baseline interaction preceded by a Multiple Imputation step for patients without post-baseline measurement.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred, worsened or became serious between the first study treatment intake date (included) and the last visit.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|--------------------------------|------------------------|
| Reporting group title | S201086/GLPG1972 75mg |
| Reporting group description: - | |
| Reporting group title | S201086/GLPG1972 150mg |
| Reporting group description: - | |
| Reporting group title | S201086/GLPG1972 300mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Serious adverse events | S201086/GLPG1972 75mg | S201086/GLPG1972 150mg | S201086/GLPG1972 300mg |
|---|--------------------------|---------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 234 (7.26%) | 17 / 231 (7.36%) | 18 / 232 (7.76%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Glottis carcinoma | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intraductal proliferative breast lesion | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 3 / 231 (1.30%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive papillary breast carcinoma | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (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 |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Prostate cancer stage II | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (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 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Face injury | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Femur fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 231 (0.43%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 231 (0.43%) | 0 / 232 (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 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical cord compression | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 234 (0.85%) | 1 / 231 (0.43%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (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 |
| Eye disorders | | | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular degeneration | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal incarcerated hernia | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Food poisoning | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Nausea | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Peritoneal cyst | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (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 |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (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 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 1 / 231 (0.43%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Myopathy | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 2 / 231 (0.87%) | 3 / 232 (1.29%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendiceal abscess | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Bronchitis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 0 / 232 (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 |
| Burn infection | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 0 / 232 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 1 / 231 (0.43%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | 0 / 231 (0.00%) | 1 / 232 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 231 (0.00%) | 0 / 232 (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 |

| Serious adverse events | Placebo | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 234 (7.69%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glottis carcinoma | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intraductal proliferative breast lesion | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Invasive papillary breast carcinoma | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer stage II | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal haemorrhage | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Face injury | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint dislocation | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery stenosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical cord compression | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Macular degeneration | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal incarcerated hernia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Nausea | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritoneal cyst | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myopathy | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendiceal abscess | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Burn infection | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| COVID-19 | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 234 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | S201086/GLPG1972 75mg | S201086/GLPG1972 150mg | S201086/GLPG1972 300mg |
|---|--------------------------|---------------------------|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 171 / 234 (73.08%) | 176 / 231 (76.19%) | 170 / 232 (73.28%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 4 / 234 (1.71%) | 3 / 231 (1.30%) | 10 / 232 (4.31%) |
| occurrences (all) | 4 | 4 | 10 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 234 (1.71%) | 2 / 231 (0.87%) | 10 / 232 (4.31%) |
| occurrences (all) | 4 | 2 | 10 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 12 / 234 (5.13%) | 7 / 231 (3.03%) | 9 / 232 (3.88%) |
| occurrences (all) | 12 | 7 | 9 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 231 (0.43%) | 9 / 232 (3.88%) |
| occurrences (all) | 1 | 1 | 9 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 3 / 234 (1.28%) | 2 / 231 (0.87%) | 16 / 232 (6.90%) |
| occurrences (all) | 3 | 2 | 16 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 4 / 234 (1.71%) | 7 / 231 (3.03%) | 6 / 232 (2.59%) |
| occurrences (all) | 6 | 8 | 6 |
| Fall | | | |
| subjects affected / exposed | 14 / 234 (5.98%) | 20 / 231 (8.66%) | 16 / 232 (6.90%) |
| occurrences (all) | 16 | 23 | 17 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 234 (2.56%) | 9 / 231 (3.90%) | 12 / 232 (5.17%) |
| occurrences (all) | 6 | 9 | 13 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 15 / 234 (6.41%) | 12 / 231 (5.19%) | 11 / 232 (4.74%) |
| occurrences (all) | 16 | 14 | 11 |
| General disorders and administration site conditions | | | |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| Oedema peripheral subjects affected / exposed occurrences (all) | 6 / 234 (2.56%) 6 | 4 / 231 (1.73%) 4 | 2 / 232 (0.86%) 2 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 234 (1.28%) 3 | 7 / 231 (3.03%) 7 | 4 / 232 (1.72%) 5 |
| Nausea subjects affected / exposed occurrences (all) | 3 / 234 (1.28%) 3 | 7 / 231 (3.03%) 8 | 11 / 232 (4.74%) 12 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 26 / 234 (11.11%) 30 | 34 / 231 (14.72%) 39 | 26 / 232 (11.21%) 31 |
| Back pain subjects affected / exposed occurrences (all) | 11 / 234 (4.70%) 12 | 10 / 231 (4.33%) 10 | 6 / 232 (2.59%) 6 |
| Joint swelling subjects affected / exposed occurrences (all) | 3 / 234 (1.28%) 3 | 7 / 231 (3.03%) 7 | 4 / 232 (1.72%) 4 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 3 / 234 (1.28%) 4 | 4 / 231 (1.73%) 5 | 8 / 232 (3.45%) 8 |
| Osteoarthritis subjects affected / exposed occurrences (all) | 6 / 234 (2.56%) 6 | 10 / 231 (4.33%) 11 | 8 / 232 (3.45%) 8 |
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 234 (2.14%) 5 | 7 / 231 (3.03%) 7 | 6 / 232 (2.59%) 6 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 8 / 234 (3.42%) 9 | 7 / 231 (3.03%) 7 | 5 / 232 (2.16%) 5 |
| Influenza subjects affected / exposed occurrences (all) | 8 / 234 (3.42%) 8 | 4 / 231 (1.73%) 4 | 3 / 232 (1.29%) 3 |

| | | | |
|---|------------------------|------------------------|------------------------|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 21 / 234 (8.97%) 23 | 16 / 231 (6.93%) 16 | 22 / 232 (9.48%) 26 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 7 / 234 (2.99%) 7 | 12 / 231 (5.19%) 20 | 6 / 232 (2.59%) 7 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 6 / 234 (2.56%) 8 | 5 / 231 (2.16%) 8 | 4 / 232 (1.72%) 4 |
| Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) | 3 / 234 (1.28%) 3 | 7 / 231 (3.03%) 7 | 4 / 232 (1.72%) 4 |

| Non-serious adverse events | Placebo | | |
|--|----------------------|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 170 / 234 (72.65%) | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 7 / 234 (2.99%) 7 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 234 (2.56%) 6 | | |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 8 / 234 (3.42%) 9 | | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 2 / 234 (0.85%) 2 | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 4 / 234 (1.71%) 4 | | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|------------------------|--|--|
| Contusion subjects affected / exposed occurrences (all) | 6 / 234 (2.56%) 7 | | |
| Fall subjects affected / exposed occurrences (all) | 13 / 234 (5.56%) 16 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 16 / 234 (6.84%) 16 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 9 / 234 (3.85%) 9 | | |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) | 8 / 234 (3.42%) 8 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 7 / 234 (2.99%) 7 | | |
| Nausea subjects affected / exposed occurrences (all) | 5 / 234 (2.14%) 6 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 19 / 234 (8.12%) 20 | | |
| Back pain subjects affected / exposed occurrences (all) | 19 / 234 (8.12%) 21 | | |
| Joint swelling subjects affected / exposed occurrences (all) | 4 / 234 (1.71%) 4 | | |
| Musculoskeletal pain | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 5 / 234 (2.14%) 5 | | |
| Osteoarthritis subjects affected / exposed occurrences (all) | 10 / 234 (4.27%) 12 | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 234 (1.71%) 4 | | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 6 / 234 (2.56%) 6 | | |
| Influenza subjects affected / exposed occurrences (all) | 7 / 234 (2.99%) 7 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 20 / 234 (8.55%) 28 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 10 / 234 (4.27%) 13 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 8 / 234 (3.42%) 8 | | |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 7 / 234 (2.99%) 7 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 11 July 2018 | <ul style="list-style-type: none">-Amendment No. 1 was applicable in all countries. The main changes included:<ul style="list-style-type: none">- Increase of the age of female patients of non-childbearing potential to 50 years old instead of 40 years old (inclusion criterion n°1) (except for female patients surgically sterile) as requested by USA IRB.- Addition of information regarding the management of an overdose of S201086/GLPG1972 as requested by Health Canada.- Addition of one withdrawal criterion "delta > 60 ms over baseline value (inclusion) with regards to ECG parameters as beside the absolute values on QTcF the delta is also an important parameter to evaluate for the safety of the patient.- Implementation of an evaluation of the consistency of the primary analysis' results between Japanese patients and non-Japanese patients as recommended by the Pharmaceuticals and Medical Devices Agency (Japanese Competent Authorities). The initial randomisation list was stratified on 2 strata (Asia vs Rest of the World). In order to ensure balanced Japanese patients between treatment groups, the stratification factors of the randomisation list were modified accordingly (3 strata in the randomisation list: Japan vs South Korea/Taiwan vs Rest of the World).- Clarification of the choice of the target knee in inclusion criterion n°9. |
| 12 March 2019 | <p>Amendment No. 2 was applicable in all countries. It mainly concerned the widening of the recruitment:</p> <ul style="list-style-type: none">- Clarification and/or modification of inclusion criteria n°7, 9 and exclusion criteria n°24, 25, 27, 28, 29, 31, 32, 33, 38, 40, 44.- Update of forbidden/authorised concomitant treatments with regards to database reference. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the exceptional circumstances in relation to the COVID-19 pandemic, the Sponsor decided in accordance with competent regulatory authorities' guidelines to implement some precautionary measures in order to mitigate the risk of infection.

Notes: