

**Clinical trial results:****Efficacy and safety of 3 doses of S 38093 (2, 5 and 20 mg/day) versus placebo, in co-administration with donepezil (10 mg/day) in patients with moderate Alzheimer's Disease.****A 24-week international, multi-centre, randomised, double-blind, placebo-controlled phase IIb study.**

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2011-005862-40 |
| Trial protocol | DE AT FI ES GB SE PT SK IT PL |
| Global end of trial date | 29 January 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 04 May 2016 |
| First version publication date | 04 May 2016 |

Trial information**Trial identification**

| | |
|-----------------------|---------------|
| Sponsor protocol code | CL2-38093-012 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | Institut de Recherches Internationales Servier |
| Sponsor organisation address | 50 rue Carnot, Suresnes, France, 92284 |
| Public contact | Clinical Studies Department, Institut de Recherches Internationales Servier, 33 155724366, clinicaltrials@servier.com |
| Scientific contact | Clinical Studies Department, Institut de Recherches Internationales Servier, 33 155724366, 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 | 29 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 January 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 January 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of 3 fixed doses of S 38093 (2, 5 and 20 mg/ day) versus placebo, in co-administration with donepezil 10 mg/day, after 24 weeks of treatment, on cognitive performance measured with the ADAS-Cog 11-items in patients with moderate Alzheimer's Disease

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:

Placebo

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 04 October 2012 |
| 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: 44 |
| Country: Number of subjects enrolled | Australia: 52 |
| Country: Number of subjects enrolled | Austria: 7 |
| Country: Number of subjects enrolled | Brazil: 41 |
| Country: Number of subjects enrolled | Canada: 35 |
| Country: Number of subjects enrolled | Finland: 15 |
| Country: Number of subjects enrolled | Germany: 63 |
| Country: Number of subjects enrolled | Italy: 76 |
| Country: Number of subjects enrolled | Mexico: 48 |
| Country: Number of subjects enrolled | Poland: 130 |
| Country: Number of subjects enrolled | Portugal: 42 |
| Country: Number of subjects enrolled | Slovakia: 60 |
| Country: Number of subjects enrolled | Spain: 115 |
| Country: Number of subjects enrolled | Sweden: 11 |
| Country: Number of subjects enrolled | United Kingdom: 67 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 806 |
| EEA total number of subjects | 586 |

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) | 138 |
| From 65 to 84 years | 640 |
| 85 years and over | 28 |

Subject disposition

Recruitment

Recruitment details:

Investigators were neuropsychiatrists, neurologists or geriatricians

Pre-assignment

Screening details:

Out-patients aged 55-90 years (Amendment n°6), school education \geq 4 years, with memory impairment (DSM-IV-TR criteria for dementia of AD type and NINCDS/ADRDA criteria for probable AD), MMSE at selection = 12-20 inclusive, brain MRI at selection, identified informant, and stable donepezil 10 mg/day for at least 3 months before selection.

Period 1

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

Blinding implementation details:

The study products of identical appearance, S 38093 2 mg, S38093 5 mg, S38093 20 mg or placebo, were assigned by a balanced, non-adaptive randomisation, with stratification by country. Treatment randomisation and allocations centralised (Interactive Response System).

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------|
| Arm title | S 38093 2 mg |
|------------------|--------------|

Arm description: -

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | S 38093 2 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One oral film-coated tablet of S 38093 2 mg, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

| | |
|------------------|--------------|
| Arm title | S 38093 5 mg |
|------------------|--------------|

Arm description: -

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | S 38093 5 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One oral film-coated tablet of S 38093 5 mg, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

| | |
|------------------|---------------|
| Arm title | S 38093 20 mg |
|------------------|---------------|

Arm description: -

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------|---------------|
| Investigational medicinal product name | S 38093 20 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One oral film-coated tablet of S 38093 20 mg, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

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

Arm description: -

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

Dosage and administration details:

One oral film-coated tablet of Placebo, with a glass of water, once a day, upon waking in the morning. In addition, the patients had to take 1 tablet of donepezil (10mg) orally once daily.

| Number of subjects in period 1 | S 38093 2 mg | S 38093 5 mg | S 38093 20 mg |
|---------------------------------------|--------------|--------------|---------------|
| Started | 201 | 202 | 203 |
| Completed | 181 | 178 | 173 |
| Not completed | 20 | 24 | 30 |
| Adverse event, serious fatal | 1 | 1 | 2 |
| Adverse event, non-fatal | 8 | 12 | 12 |
| Non-medical reason | 6 | 6 | 8 |
| Lack of efficacy | 2 | - | 1 |
| Protocol deviation | 3 | 5 | 7 |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 200 |
| Completed | 181 |
| Not completed | 19 |
| Adverse event, serious fatal | 2 |
| Adverse event, non-fatal | 8 |
| Non-medical reason | 3 |
| Lack of efficacy | - |
| Protocol deviation | 6 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | S 38093 2 mg |
| Reporting group description: - | |
| Reporting group title | S 38093 5 mg |
| Reporting group description: - | |
| Reporting group title | S 38093 20 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | S 38093 2 mg | S 38093 5 mg | S 38093 20 mg |
|-------------------------------------------------------|--------------|--------------|---------------|
| Number of subjects | 201 | 202 | 203 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 31 | 39 | 29 |
| From 65-84 years | 160 | 159 | 165 |
| 85 years and over | 10 | 4 | 9 |
| Age continuous Units: years | | | |
| arithmetic mean | 72.7 | 72.1 | 73.3 |
| standard deviation | ± 7.6 | ± 7.6 | ± 7.4 |
| Gender categorical Units: Subjects | | | |
| Female | 129 | 130 | 131 |
| Male | 72 | 72 | 72 |

| Reporting group values | Placebo | Total | |
|-------------------------------------------------------|---------|-------|--|
| Number of subjects | 200 | 806 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 39 | 138 | |
| From 65-84 years | 156 | 640 | |

| | | | |
|-------------------|---|----|--|
| 85 years and over | 5 | 28 | |
|-------------------|---|----|--|

| | | | |
|-------------------------------------------------------------------------|---------------|-----|--|
| Age continuous Units: years arithmetic mean standard deviation | 72.5 ± 8.3 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 114 | 504 | |
| Male | 86 | 302 | |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients of the Randomised Set having taken at least one dose of study drug and having a value at baseline and at least one post-baseline value for the primary criterion.

| Reporting group values | Full Analysis Set | | |
|-------------------------------------------------------------------------|-------------------|--|--|
| Number of subjects | 765 | | |
| 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) | 132 | | |
| From 65-84 years | 606 | | |
| 85 years and over | 27 | | |
| Age continuous Units: years arithmetic mean standard deviation | 72.6 ± 7.7 | | |
| Gender categorical Units: Subjects | | | |
| Female | 481 | | |
| Male | 284 | | |

End points

End points reporting groups

| | |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reporting group title | S 38093 2 mg |
| Reporting group description: | - |
| Reporting group title | S 38093 5 mg |
| Reporting group description: | - |
| Reporting group title | S 38093 20 mg |
| Reporting group description: | - |
| Reporting group title | Placebo |
| Reporting group description: | - |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | All patients of the Randomised Set having taken at least one dose of study drug and having a value at baseline and at least one post-baseline value for the primary criterion. |

Primary: 11-item ADAS-Cog total score

| | |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 11-item ADAS-Cog total score |
| End point description: | |
| End point type | Primary |
| End point timeframe: | Evaluation at inclusion, week 12 and week 24 or in case of premature withdrawal. The main analytical approach was the change from baseline to W24. |

| End point values | S 38093 2 mg | S 38093 5 mg | S 38093 20 mg | Placebo |
|----------------------------------|--------------------|--------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 191 | 192 | 193 | 189 |
| Units: no unit | | | | |
| arithmetic mean (standard error) | 1.08 (\pm 5.07) | 1.08 (\pm 5.93) | 0.48 (\pm 6.26) | 0.52 (\pm 6) |

Statistical analyses

| | |
|-----------------------------------------|------------------------------------------|
| Statistical analysis title | Primary analysis |
| Comparison groups | S 38093 2 mg v Placebo |
| Number of subjects included in analysis | 380 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.72 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.48 |
| upper limit | 1.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.61 |

| | |
|-----------------------------------------|------------------------------------------|
| Statistical analysis title | Primary analysis |
| Comparison groups | S 38093 20 mg v Placebo |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.24 |
| upper limit | 1.16 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.61 |

| | |
|-----------------------------------------|------------------------------------------|
| Statistical analysis title | Primary analysis |
| Comparison groups | S 38093 5 mg v Placebo |
| Number of subjects included in analysis | 381 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Mixed-effects Model for Repeated Measure |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 1.69 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.61 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious according to the investigator, or upgraded by the Sponsor, between the first study drug intake and the last study drug intake date + 10 days (both included).

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

| | |
|------------------------------|---------------|
| Reporting group title | S 38093 2 mg |
| Reporting group description: | - |
| Reporting group title | S 38093 5 mg |
| Reporting group description: | - |
| Reporting group title | S 38093 20 mg |
| Reporting group description: | - |
| Reporting group title | Placebo |
| Reporting group description: | - |

| Serious adverse events | S 38093 2 mg | S 38093 5 mg | S 38093 20 mg |
|---------------------------------------------------------------------|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 199 (6.03%) | 15 / 200 (7.50%) | 19 / 202 (9.41%) |
| number of deaths (all causes) | 1 | 2 | 2 |
| 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 | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |

| | | | |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| Diffuse large B-cell lymphoma stage IV | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| 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 | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Surgical and medical procedures | | | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Pulmonary fibrosis | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 200 (0.50%) | 2 / 202 (0.99%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agitation | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 200 (0.50%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delusion | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | 0 / 200 (0.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressive symptom | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucinations, mixed | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 2 / 202 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Major depression | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Contusion | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Fall | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | 3 / 200 (1.50%) | 3 / 202 (1.49%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Head injury | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 200 (0.50%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Ligament rupture | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 fume inhalation disorder | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular procedure complication | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Wound | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Wrist fracture | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive disorder | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 2 / 202 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Grand mal convulsion | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Paraesthesia | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Parkinsonism | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| 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 | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 5 / 202 (2.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 | | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 2 / 200 (1.00%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Panniculitis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 failure | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Infections and infestations | | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Erysipelas | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Herpes simplex encephalitis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 2 / 202 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Post procedural sepsis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 1 / 202 (0.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 0 / 200 (0.00%) | 2 / 202 (0.99%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 0 / 202 (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 |

| Serious adverse events | Placebo | | |
|----------------------------------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 199 (11.56%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diffuse large B-cell lymphoma stage IV | | | |

| | | | |
|-------------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Hip arthroplasty | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary fibrosis | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Delusion | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depressive symptom | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hallucination | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hallucinations, mixed | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Major depression | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| Contusion | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral neck fracture | | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head injury | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Joint dislocation | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ligament rupture | | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory fume inhalation disorder | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular procedure complication | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Angina unstable | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cognitive disorder | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dementia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paraesthesia | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Parkinsonism | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Panniculitis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| Renal failure | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|-------------------------------------------------|-----------------|--|--|--|
| Erysipelas | | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes simplex encephalitis | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonsillar abscess | | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post procedural sepsis | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative wound infection | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection bacterial | | | | |

| | | | |
|-------------------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 199 (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 / 199 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1.5 %

| Non-serious adverse events | S 38093 2 mg | S 38093 5 mg | S 38093 20 mg |
|--------------------------------------------------------------|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 102 / 199 (51.26%) | 106 / 200 (53.00%) | 101 / 202 (50.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 199 (2.51%) | 1 / 200 (0.50%) | 3 / 202 (1.49%) |
| occurrences (all) | 5 | 1 | 3 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 0 / 200 (0.00%) | 2 / 202 (0.99%) |
| occurrences (all) | 0 | 0 | 2 |
| Surgical and medical procedures | | | |
| Cataract operation | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 3 / 200 (1.50%) | 0 / 202 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 5 / 200 (2.50%) | 1 / 202 (0.50%) |
| occurrences (all) | 1 | 5 | 1 |
| Fatigue | | | |

| | | | |
|-----------------------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 199 (1.01%) 2 | 0 / 200 (0.00%) 0 | 5 / 202 (2.48%) 6 |
| Gait disturbance subjects affected / exposed occurrences (all) | 2 / 199 (1.01%) 2 | 2 / 200 (1.00%) 2 | 0 / 202 (0.00%) 0 |
| Psychiatric disorders | | | |
| Aggression subjects affected / exposed occurrences (all) | 7 / 199 (3.52%) 7 | 0 / 200 (0.00%) 0 | 1 / 202 (0.50%) 1 |
| Agitation subjects affected / exposed occurrences (all) | 0 / 199 (0.00%) 0 | 1 / 200 (0.50%) 1 | 6 / 202 (2.97%) 6 |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 199 (1.01%) 2 | 5 / 200 (2.50%) 5 | 3 / 202 (1.49%) 3 |
| Depression subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 4 | 2 / 200 (1.00%) 2 | 0 / 202 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 4 | 1 / 200 (0.50%) 1 | 2 / 202 (0.99%) 2 |
| Irritability subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 4 | 2 / 200 (1.00%) 2 | 3 / 202 (1.49%) 3 |
| Nightmare subjects affected / exposed occurrences (all) | 2 / 199 (1.01%) 2 | 1 / 200 (0.50%) 1 | 1 / 202 (0.50%) 1 |
| Investigations | | | |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 199 (0.00%) 0 | 1 / 200 (0.50%) 1 | 1 / 202 (0.50%) 1 |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 199 (1.01%) 2 | 2 / 200 (1.00%) 2 | 5 / 202 (2.48%) 5 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--------------------------------------|-----------------|------------------|------------------|
| Contusion | | | |
| subjects affected / exposed | 1 / 199 (0.50%) | 1 / 200 (0.50%) | 5 / 202 (2.48%) |
| occurrences (all) | 1 | 1 | 5 |
| Fall | | | |
| subjects affected / exposed | 5 / 199 (2.51%) | 13 / 200 (6.50%) | 11 / 202 (5.45%) |
| occurrences (all) | 8 | 13 | 11 |
| Head injury | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 3 / 200 (1.50%) | 0 / 202 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | 4 / 200 (2.00%) | 8 / 202 (3.96%) |
| occurrences (all) | 4 | 7 | 8 |
| Headache | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | 7 / 200 (3.50%) | 7 / 202 (3.47%) |
| occurrences (all) | 4 | 9 | 7 |
| Somnolence | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | 0 / 200 (0.00%) | 3 / 202 (1.49%) |
| occurrences (all) | 3 | 0 | 3 |
| Tension headache | | | |
| subjects affected / exposed | 0 / 199 (0.00%) | 1 / 200 (0.50%) | 0 / 202 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | 0 / 200 (0.00%) | 1 / 202 (0.50%) |
| occurrences (all) | 2 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 199 (4.02%) | 1 / 200 (0.50%) | 4 / 202 (1.98%) |
| occurrences (all) | 9 | 1 | 5 |
| Nausea | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | 5 / 200 (2.50%) | 8 / 202 (3.96%) |
| occurrences (all) | 4 | 5 | 9 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | 5 / 200 (2.50%) | 2 / 202 (0.99%) |
| occurrences (all) | 2 | 5 | 2 |
| Renal and urinary disorders | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------|------------------------|-----------------------|----------------------|
| Haematuria subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 4 | 1 / 200 (0.50%) 1 | 1 / 202 (0.50%) 1 |
| Leukocyturia subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 5 | 7 / 200 (3.50%) 7 | 7 / 202 (3.47%) 7 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 199 (0.00%) 0 | 1 / 200 (0.50%) 1 | 5 / 202 (2.48%) 5 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 3 / 199 (1.51%) 3 | 1 / 200 (0.50%) 1 | 0 / 202 (0.00%) 0 |
| Infections and infestations Asymptomatic bacteriuria subjects affected / exposed occurrences (all) | 1 / 199 (0.50%) 1 | 4 / 200 (2.00%) 4 | 3 / 202 (1.49%) 3 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 4 | 2 / 200 (1.00%) 2 | 0 / 202 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 4 | 7 / 200 (3.50%) 9 | 3 / 202 (1.49%) 3 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 199 (1.01%) 2 | 1 / 200 (0.50%) 1 | 6 / 202 (2.97%) 6 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 13 / 199 (6.53%) 15 | 9 / 200 (4.50%) 10 | 7 / 202 (3.47%) 7 |
| Urinary tract infection bacterial subjects affected / exposed occurrences (all) | 5 / 199 (2.51%) 6 | 4 / 200 (2.00%) 4 | 2 / 202 (0.99%) 2 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 3 / 199 (1.51%) 3 | 2 / 200 (1.00%) 2 | 2 / 202 (0.99%) 2 |

| | | | |
|---------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 3 / 199 (1.51%) 3 | 4 / 200 (2.00%) 4 | 4 / 202 (1.98%) 4 |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 3 / 199 (1.51%) 3 | 4 / 200 (2.00%) 4 | 1 / 202 (0.50%) 1 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 3 / 199 (1.51%) 3 | 0 / 200 (0.00%) 0 | 0 / 202 (0.00%) 0 |

| Non-serious adverse events | Placebo | | |
|----------------------------------------------------------------------------------------------------------------------|----------------------|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 113 / 199 (56.78%) | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 5 | | |
| Hypotension subjects affected / exposed occurrences (all) | 4 / 199 (2.01%) 4 | | |
| Surgical and medical procedures Cataract operation subjects affected / exposed occurrences (all) | 0 / 199 (0.00%) 0 | | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 0 / 199 (0.00%) 0 | | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 199 (0.00%) 0 | | |
| Gait disturbance subjects affected / exposed occurrences (all) | 3 / 199 (1.51%) 3 | | |
| Psychiatric disorders Aggression | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| <p>subjects affected / exposed occurrences (all)</p> <p>Agitation</p> <p>subjects affected / exposed occurrences (all)</p> <p>Anxiety</p> <p>subjects affected / exposed occurrences (all)</p> <p>Depression</p> <p>subjects affected / exposed occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed occurrences (all)</p> <p>Irritability</p> <p>subjects affected / exposed occurrences (all)</p> <p>Nightmare</p> <p>subjects affected / exposed occurrences (all)</p> | <p>4 / 199 (2.01%) 4</p> <p>6 / 199 (3.02%) 6</p> <p>4 / 199 (2.01%) 4</p> <p>1 / 199 (0.50%) 1</p> <p>3 / 199 (1.51%) 3</p> <p>2 / 199 (1.01%) 2</p> <p>4 / 199 (2.01%) 5</p> | | |
| <p>Investigations</p> <p>Blood creatine phosphokinase increased</p> <p>subjects affected / exposed occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed occurrences (all)</p> | <p>3 / 199 (1.51%) 3</p> <p>3 / 199 (1.51%) 3</p> | | |
| <p>Injury, poisoning and procedural complications</p> <p>Contusion</p> <p>subjects affected / exposed occurrences (all)</p> <p>Fall</p> <p>subjects affected / exposed occurrences (all)</p> <p>Head injury</p> | <p>0 / 199 (0.00%) 0</p> <p>5 / 199 (2.51%) 5</p> | | |

| | | | |
|--------------------------------------------------|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 199 (0.50%) 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 199 (3.02%) | | |
| occurrences (all) | 7 | | |
| Headache | | | |
| subjects affected / exposed | 7 / 199 (3.52%) | | |
| occurrences (all) | 8 | | |
| Somnolence | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences (all) | 2 | | |
| Tension headache | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences (all) | 3 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences (all) | 3 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 199 (2.51%) | | |
| occurrences (all) | 5 | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences (all) | 2 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 3 / 199 (1.51%) | | |
| occurrences (all) | 3 | | |
| Leukocyturia | | | |
| subjects affected / exposed | 4 / 199 (2.01%) | | |
| occurrences (all) | 4 | | |
| Urinary incontinence | | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 199 (0.50%) 1 | | |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 0 / 199 (0.00%) 0 | | |
| Infections and infestations Asymptomatic bacteriuria subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Urinary tract infection bacterial subjects affected / exposed occurrences (all) | 3 / 199 (1.51%) 3 0 / 199 (0.00%) 0 7 / 199 (3.52%) 9 1 / 199 (0.50%) 1 9 / 199 (4.52%) 9 5 / 199 (2.51%) 9 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypercholesterolaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all) Hypokalaemia | 5 / 199 (2.51%) 5 1 / 199 (0.50%) 1 3 / 199 (1.51%) 3 0 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 199 (1.01%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 March 2013 | The non-inclusion criteria referring to the ECG findings (PR < 280 ms was replaced by PR > 280 ms) were corrected. New laboratory assessments (LDL and HDL, in order to complete the lipid metabolism analysis already done with the total cholesterol) were introduced. Anticipated benefits/risks and conditions of use of forbidden concomitant treatment were added in the "background" section. Some scale instructions and worksheets to be used in this study were finalized. |
| 03 July 2013 | Withdrawal criterion was updated in accordance with the last version of the Summary of Product Characteristics for donepezil. |
| 13 December 2013 | The selection criteria referring to age were updated to include very old patients with Alzheimer's disease (the upper limit to participate to the study was changed from 85 to 90 years old, both inclusive). In order to get a more accurate value for the inclusion of patients, 3 ECGs in close succession were to be performed at the selection visit (ASSE) instead of one. The MRI criteria were updated to allow the inclusion of patients with cerebrovascular disease, a common radiological finding, especially in the elderly, as long as the cerebrovascular lesions were unlikely to contribute to the dementia syndrome. Change in authorised concomitant treatment (antipsychotic treatment with typical or atypical neuroleptics was prohibited anymore before and during the study). |
| 15 April 2014 | Due to strategic reasons and recruitment difficulties, the number of planned included patients was updated (around 700 instead of 1000). |
| 22 July 2014 | New safety data and information regarding the stage of the other studies, in particular the phase IIb monotherapy study which was ended (CL2-38093-011) were added in the "background" section. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported