



Clinical trial results:

Dose-finding of semaglutide administered subcutaneously once daily versus placebo and liraglutide in subjects with type 2 diabetes

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-003196-39 |
| Trial protocol | GB DE CZ AT |
| Global end of trial date | 13 October 2016 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 27 October 2017 |
| First version publication date | 27 October 2017 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN9535-4191 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02461589 |
| WHO universal trial number (UTN) | U1111-1159-4923 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novo Nordisk A/S |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880 |
| Public contact | Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact | Global Clinical Registry (GCR, 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 May 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 October 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 October 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of four dose-levels of semaglutide administered subcutaneously (s.c.) once daily (OD) versus placebo on glycaemic control after 26 weeks of treatment

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and EN ISO 14155 Part 1 and 2, and 21 CFR 312.120.

Background therapy:

Subjects continued the pre-trial stable diabetes treatment consisting of diet and exercise with or without metformin (≥ 1500 mg daily or maximum tolerated dose) during the trial.

Evidence for comparator:

Not applicable

| | |
|---|-------------------|
| Actual start date of recruitment | 21 September 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Austria: 31 |
| Country: Number of subjects enrolled | Canada: 39 |
| Country: Number of subjects enrolled | Czech Republic: 53 |
| Country: Number of subjects enrolled | Germany: 42 |
| Country: Number of subjects enrolled | United Kingdom: 76 |
| Country: Number of subjects enrolled | Malaysia: 31 |
| Country: Number of subjects enrolled | Russian Federation: 50 |
| Country: Number of subjects enrolled | Serbia: 84 |
| Country: Number of subjects enrolled | United States: 239 |
| Country: Number of subjects enrolled | South Africa: 60 |
| Worldwide total number of subjects | 705 |
| EEA total number of subjects | 202 |

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) | 550 |
| From 65 to 84 years | 155 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 139 sites in 10 countries as follows:

Austria: 3 sites; Canada: 8 sites; Czech Republic: 9 sites; Germany:

7 sites; Malaysia: 5 sites; Russian Federation: 7 sites; Serbia: 9

sites; South Africa: 7 sites; United Kingdom: 13 sites; United States: 71 sites.

Pre-assignment

Screening details:

Not applicable

Period 1

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

Blinding implementation details:

A portion of this trial was double-blinded (sponsor, investigators, and subjects) within dose level in order to minimise bias during trial conduct. Semaglutide, liraglutide, and placebo were visually identical to fulfil the requirements for double-blind procedures. Furthermore, equal volumes of semaglutide, liraglutide, and placebo were administered during treatment ensuring blinding within dose-level. An open-label design was chosen for the semaglutide flexible dose arm of the trial.

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Semaglutide 0.05 mg |

Arm description:

Participants received semaglutide 0.05 mg sc injection once daily for 26 weeks.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with semaglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|--------------------|
| Arm title | Semaglutide 0.1 mg |
|------------------|--------------------|

Arm description:

Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily upto week 26.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with semaglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|--------------------|
| Arm title | Semaglutide 0.2 mg |
|------------------|--------------------|

Arm description:

Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks and then semaglutide 0.2 mg once daily upto week 26.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with semaglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|--------------------|
| Arm title | Semaglutide 0.3 mg |
|------------------|--------------------|

Arm description:

Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks sequentially followed by 0.2 mg once daily for next 4 weeks and then semaglutide 0.3 mg once daily upto week 26.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with semaglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|--------------------|
| Arm title | Liraglutide 0.3 mg |
|------------------|--------------------|

Arm description:

Participants received liraglutide 0.3 mg sc injection once daily for 26 weeks.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza® |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with liraglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|--------------------|
| Arm title | Liraglutide 0.6 mg |
|------------------|--------------------|

Arm description:

Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily upto week 26.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza® |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with liraglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|--------------------|
| Arm title | Liraglutide 1.2 mg |
|------------------|--------------------|

Arm description:

Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily for next 4 weeks and then liraglutide 1.2 mg once daily upto week 26.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza® |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with liraglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|--------------------|
| Arm title | Liraglutide 1.8 mg |
|------------------|--------------------|

Arm description:

Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily for next 4 weeks sequentially followed by liraglutide 1.2 mg once daily for next 4 weeks and then liraglutide 1.8 mg once daily upto week 26.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | Victoza® |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with liraglutide sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

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

Arm description:

Participants received placebo (equal volumes as semaglutide or liraglutide) sc injection once daily upto 26 weeks.

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

Dosage and administration details:

Participants were administered with placebo sc injection in the thigh, abdomen, or upper arm, using a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| | |
|------------------|----------------------|
| Arm title | Semaglutide flexible |
|------------------|----------------------|

Arm description:

Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks sequentially followed by 0.2 mg once daily for next 4 weeks and then semaglutide 0.3 mg once daily upto week 26. Participants were allowed to follow a more flexible dose-escalation regimen. Semaglutide dose levels could be temporarily reduced in participants with poor gastrointestinal tolerability depending on investigator's assessment.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Participants were administered with semaglutide sc injection in the thigh, abdomen, or upper arm, using

a durable pen injector (NovoPen® 4) preferably around the same time of the day irrespective of meals.

| Number of subjects in period 1 | Semaglutide 0.05 mg | Semaglutide 0.1 mg | Semaglutide 0.2 mg |
|---------------------------------------|---------------------|--------------------|--------------------|
| Started | 64 | 63 | 65 |
| Completed | 58 | 61 | 60 |
| Not completed | 6 | 2 | 5 |
| Adverse event, serious fatal | - | - | - |
| Consent withdrawn by subject | 5 | 1 | 3 |
| Unclassified | - | - | - |
| Lost to follow-up | - | - | 2 |
| Missing follow-up information | 1 | 1 | - |

| Number of subjects in period 1 | Semaglutide 0.3 mg | Liraglutide 0.3 mg | Liraglutide 0.6 mg |
|---------------------------------------|--------------------|--------------------|--------------------|
| Started | 63 | 64 | 64 |
| Completed | 58 | 62 | 61 |
| Not completed | 5 | 2 | 3 |
| Adverse event, serious fatal | - | - | - |
| Consent withdrawn by subject | 2 | 1 | 2 |
| Unclassified | - | - | - |
| Lost to follow-up | 3 | 1 | 1 |
| Missing follow-up information | - | - | - |

| Number of subjects in period 1 | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Placebo |
|---------------------------------------|--------------------|--------------------|---------|
| Started | 64 | 65 | 129 |
| Completed | 58 | 60 | 123 |
| Not completed | 6 | 5 | 6 |
| Adverse event, serious fatal | - | 1 | - |
| Consent withdrawn by subject | 1 | 3 | 3 |
| Unclassified | 1 | - | - |
| Lost to follow-up | 3 | 1 | 3 |
| Missing follow-up information | 1 | - | - |

| Number of subjects in period 1 | Semaglutide flexible |
|---------------------------------------|----------------------|
| Started | 64 |
| Completed | 60 |
| Not completed | 4 |

| | |
|-------------------------------|---|
| Adverse event, serious fatal | - |
| Consent withdrawn by subject | 1 |
| Unclassified | 2 |
| Lost to follow-up | 1 |
| Missing follow-up information | - |

Baseline characteristics

| Reporting groups | |
|---|----------------------|
| Reporting group title | Semaglutide 0.05 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 26 weeks. | |
| Reporting group title | Semaglutide 0.1 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily upto week 26. | |
| Reporting group title | Semaglutide 0.2 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks and then semaglutide 0.2 mg once daily upto week 26. | |
| Reporting group title | Semaglutide 0.3 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks sequentially followed by 0.2 mg once daily for next 4 weeks and then semaglutide 0.3 mg once daily upto week 26. | |
| Reporting group title | Liraglutide 0.3 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 26 weeks. | |
| Reporting group title | Liraglutide 0.6 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily upto week 26. | |
| Reporting group title | Liraglutide 1.2 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily for next 4 weeks and then liraglutide 1.2 mg once daily upto week 26. | |
| Reporting group title | Liraglutide 1.8 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily for next 4 weeks sequentially followed by liraglutide 1.2 mg once daily for next 4 weeks and then liraglutide 1.8 mg once daily upto week 26. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received placebo (equal volumes as semaglutide or liraglutide) sc injection once daily upto 26 weeks. | |
| Reporting group title | Semaglutide flexible |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks sequentially followed by 0.2 mg once daily for next 4 weeks and then semaglutide 0.3 mg once daily upto week 26. Participants were allowed to follow a more flexible dose-escalation regimen. Semaglutide dose levels could be temporarily reduced in participants with poor gastrointestinal tolerability depending on investigator's assessment. | |

| Reporting group values | Semaglutide 0.05 mg | Semaglutide 0.1 mg | Semaglutide 0.2 mg |
|------------------------------------|---------------------|--------------------|--------------------|
| Number of subjects | 64 | 63 | 65 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 49 | 45 | 44 |
| From 65-84 years | 15 | 18 | 21 |

| | | | |
|---|-------------------|-------------------|-------------------|
| Age Continuous Units: years arithmetic mean standard deviation | 57.53 ± 9.8 | 57.51 ± 10.0 | 58.37 ± 9.58 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 31 | 28 | 22 |
| Male | 33 | 35 | 43 |
| Study Specific Characteristic glycosylated haemoglobin (HbA1c) Units: percentage of HbA1c arithmetic mean standard deviation | 7.87 ± 0.71 | 7.91 ± 0.83 | 7.96 ± 0.82 |
| Study Specific Characteristic Fasting plasma glucose Units: mmol/L arithmetic mean standard deviation | 9.26 ± 2.60 | 8.97 ± 2.22 | 9.20 ± 2.28 |
| Study Specific Characteristic Body weight Units: kg arithmetic mean standard deviation | 93.44 ± 18.27 | 92.40 ± 17.20 | 98.07 ± 17.92 |
| Study Specific Characteristic Systolic blood pressure Units: mmHg arithmetic mean standard deviation | 133.70 ± 15.14 | 130.97 ± 14.92 | 131.34 ± 12.55 |
| Study Specific Characteristic Diastolic blood pressure Units: mmHg arithmetic mean standard deviation | 80.06 ± 8.90 | 79.71 ± 8.56 | 80.48 ± 8.87 |

| Reporting group values | Semaglutide 0.3 mg | Liraglutide 0.3 mg | Liraglutide 0.6 mg |
|---|--------------------|--------------------|--------------------|
| Number of subjects | 63 | 64 | 64 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 54 | 47 | 46 |
| From 65-84 years | 9 | 17 | 18 |
| Age Continuous Units: years arithmetic mean standard deviation | 54.76 ± 9.66 | 57.20 ± 10.78 | 59.45 ± 9.77 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 31 | 35 | 32 |
| Male | 32 | 29 | 32 |
| Study Specific Characteristic glycosylated haemoglobin (HbA1c) Units: percentage of HbA1c arithmetic mean standard deviation | 8.23 ± 0.80 | 8.06 ± 0.86 | 8.12 ± 0.81 |

| | | | |
|--|-------------------|-------------------|-------------------|
| Study Specific Characteristic Fasting plasma glucose Units: mmol/L arithmetic mean standard deviation | 9.67 ± 2.56 | 9.32 ± 2.54 | 9.34 ± 2.33 |
| Study Specific Characteristic Body weight Units: kg arithmetic mean standard deviation | 94.82 ± 17.84 | 92.25 ± 17.48 | 92.68 ± 16.46 |
| Study Specific Characteristic Systolic blood pressure Units: mmHg arithmetic mean standard deviation | 132.08 ± 11.69 | 134.02 ± 11.30 | 132.41 ± 12.37 |
| Study Specific Characteristic Diastolic blood pressure Units: mmHg arithmetic mean standard deviation | 81.41 ± 8.05 | 81.83 ± 6.98 | 81.28 ± 6.90 |

| Reporting group values | Liraglutide 1.2 mg | Liraglutide 1.8 mg | Placebo |
|---|--------------------|--------------------|------------------|
| Number of subjects | 64 | 65 | 129 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 54 | 51 | 105 |
| From 65-84 years | 10 | 14 | 24 |
| Age Continuous Units: years arithmetic mean standard deviation | 53.73 ± 11.35 | 55.82 ± 9.19 | 57.08 ± 9.25 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 30 | 32 | 57 |
| Male | 34 | 33 | 72 |
| Study Specific Characteristic glycosylated haemoglobin (HbA1c) Units: percentage of HbA1c arithmetic mean standard deviation | 8.14 ± 0.87 | 8.07 ± 0.85 | 8.12 ± 0.87 |
| Study Specific Characteristic Fasting plasma glucose Units: mmol/L arithmetic mean standard deviation | 9.91 ± 2.70 | 9.18 ± 2.45 | 9.67 ± 2.98 |
| Study Specific Characteristic Body weight Units: kg arithmetic mean standard deviation | 96.67 ± 18.28 | 93.40 ± 19.34 | 93.98 ± 17.75 |
| Study Specific Characteristic Systolic blood pressure Units: mmHg arithmetic mean | 134.20 | 131.02 | 132.17 |

| | | | |
|--|---------|---------|---------|
| standard deviation | ± 12.73 | ± 11.86 | ± 14.26 |
| Study Specific Characteristic Diastolic blood pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 82.98 | 80.66 | 80.98 |
| standard deviation | ± 6.94 | ± 7.62 | ± 8.00 |

| Reporting group values | Semaglutide flexible | Total | |
|--|----------------------|-------|--|
| Number of subjects | 64 | 705 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 55 | 550 | |
| From 65-84 years | 9 | 155 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.81 | | |
| standard deviation | ± 9.70 | - | |
| Gender, Male/Female | | | |
| Units: Subjects | | | |
| Female | 28 | 326 | |
| Male | 36 | 379 | |
| Study Specific Characteristic glycosylated haemoglobin (HbA1c) | | | |
| Units: percentage of HbA1c | | | |
| arithmetic mean | 8.10 | | |
| standard deviation | ± 0.91 | - | |
| Study Specific Characteristic Fasting plasma glucose | | | |
| Units: mmol/L | | | |
| arithmetic mean | 9.82 | | |
| standard deviation | ± 2.66 | - | |
| Study Specific Characteristic Body weight | | | |
| Units: kg | | | |
| arithmetic mean | 95.29 | | |
| standard deviation | ± 15.43 | - | |
| Study Specific Characteristic Systolic blood pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 132.70 | | |
| standard deviation | ± 12.74 | - | |
| Study Specific Characteristic Diastolic blood pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 81.89 | | |
| standard deviation | ± 8.40 | - | |

End points

End points reporting groups

| | |
|---|----------------------|
| Reporting group title | Semaglutide 0.05 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 26 weeks. | |
| Reporting group title | Semaglutide 0.1 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily upto week 26. | |
| Reporting group title | Semaglutide 0.2 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks and then semaglutide 0.2 mg once daily upto week 26. | |
| Reporting group title | Semaglutide 0.3 mg |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks sequentially followed by 0.2 mg once daily for next 4 weeks and then semaglutide 0.3 mg once daily upto week 26. | |
| Reporting group title | Liraglutide 0.3 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 26 weeks. | |
| Reporting group title | Liraglutide 0.6 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily upto week 26. | |
| Reporting group title | Liraglutide 1.2 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily for next 4 weeks and then liraglutide 1.2 mg once daily upto week 26. | |
| Reporting group title | Liraglutide 1.8 mg |
| Reporting group description: Participants received liraglutide 0.3 mg sc injection once daily for 4 weeks followed by liraglutide 0.6 mg once daily for next 4 weeks sequentially followed by liraglutide 1.2 mg once daily for next 4 weeks and then liraglutide 1.8 mg once daily upto week 26. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received placebo (equal volumes as semaglutide or liraglutide) sc injection once daily upto 26 weeks. | |
| Reporting group title | Semaglutide flexible |
| Reporting group description: Participants received semaglutide 0.05 mg sc injection once daily for 4 weeks followed by semaglutide 0.1 mg once daily for next 4 weeks sequentially followed by 0.2 mg once daily for next 4 weeks and then semaglutide 0.3 mg once daily upto week 26. Participants were allowed to follow a more flexible dose-escalation regimen. Semaglutide dose levels could be temporarily reduced in participants with poor gastrointestinal tolerability depending on investigator's assessment. | |

Primary: Change in HbA1c (Glycosylated haemoglobin)

| | |
|---|--|
| End point title | Change in HbA1c (Glycosylated haemoglobin) |
| End point description: Mean change from baseline in HbA1c at week 26. The full analysis set (FAS) included all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS would contribute to the evaluation "as randomised". | |

Analysis was performed using a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Week 0, week 26 | |

| End point values | Semaglutide 0.05 mg | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.3 mg |
|--------------------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 63 | 65 | 63 |
| Units: percentage of HbA1c | | | | |
| arithmetic mean (standard deviation) | -0.97 (± 0.85) | -1.30 (± 1.03) | -1.65 (± 0.79) | -1.96 (± 0.95) |

| End point values | Liraglutide 0.3 mg | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 64 | 64 | 65 |
| Units: percentage of HbA1c | | | | |
| arithmetic mean (standard deviation) | -0.50 (± 0.93) | -0.88 (± 0.90) | -0.86 (± 0.92) | -1.32 (± 0.78) |

| End point values | Placebo | Semaglutide flexible | | |
|--------------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 129 | 64 | | |
| Units: percentage of HbA1c | | | | |
| arithmetic mean (standard deviation) | -0.05 (± 0.90) | -1.72 (± 0.97) | | |

Statistical analyses

| | |
|--|-------------------------------|
| Statistical analysis title | Semaglutide 0.05 vs placebo |
| Statistical analysis description: | |
| Analysis was performed using a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit. | |
| Comparison groups | Semaglutide 0.05 mg v Placebo |
| Number of subjects included in analysis | 193 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.04 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | -0.77 |

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Semaglutide 0.1 vs placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

Analysis was performed using a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit.

| | |
|---|------------------------------|
| Comparison groups | Semaglutide 0.1 mg v Placebo |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.61 |
| upper limit | -1.08 |

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Semaglutide 0.2 vs placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

Analysis was performed using a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit.

| | |
|---|------------------------------|
| Comparison groups | Semaglutide 0.2 mg v Placebo |
| Number of subjects included in analysis | 194 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.95 |
| upper limit | -1.42 |

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Semaglutide 0.3 vs placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

Analysis was performed using a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit.

| | |
|---|------------------------------|
| Comparison groups | Semaglutide 0.3 mg v Placebo |
| Number of subjects included in analysis | 192 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.12 |
| upper limit | -1.6 |

Secondary: Change in Fasting plasma glucose (FPG)

| | |
|--|--|
| End point title | Change in Fasting plasma glucose (FPG) |
| End point description: | |
| Mean change from baseline in FPG at week 26. | |
| The FAS included all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS would contribute to the evaluation "as randomised". | |
| Analysis was performed using a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 0, Week 26 | |

| End point values | Semaglutide 0.05 mg | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.3 mg |
|--------------------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 63 | 65 | 63 |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -2.09 (± 1.96) | -2.08 (± 2.23) | -2.64 (± 2.07) | -3.53 (± 2.20) |

| End point values | Liraglutide 0.3 mg | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 64 | 64 | 65 |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -1.33 (± 2.06) | -1.56 (± 1.74) | -1.51 (± 2.41) | -1.92 (± 2.34) |

| End point values | Placebo | Semaglutide flexible | | |
|--------------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 129 | 63 | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | -0.54 (± 2.45) | -3.40 (± 2.84) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Body weight change

| | |
|---|--------------------|
| End point title | Body weight change |
| End point description: | |
| Mean change from baseline in body weight at week 26. | |
| The FAS included all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS would contribute to the evaluation "as randomised". Missing data imputed from a mixed model for repeated measures with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit. | |
| End point type | Secondary |
| End point timeframe: | |
| Week 0, Week 26 | |

| End point values | Semaglutide 0.05 mg | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.3 mg |
|--------------------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 63 | 65 | 63 |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | -2.75 (± 2.82) | -4.36 (± 4.24) | -6.70 (± 4.57) | -8.23 (± 5.34) |

| End point values | Liraglutide 0.3 mg | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 64 | 64 | 65 |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | -1.48 (± 3.06) | -1.81 (± 3.06) | -1.78 (± 3.41) | -3.68 (± 4.26) |

| End point values | Placebo | Semaglutide flexible | | |
|--------------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 129 | 64 | | |
| Units: kg | | | | |
| arithmetic mean (standard deviation) | -1.22 (± 3.42) | -6.60 (± 4.98) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Systolic and diastolic blood pressure

| | |
|-----------------|---|
| End point title | Change in Systolic and diastolic blood pressure |
|-----------------|---|

End point description:

Mean change from baseline in blood pressure (systolic and diastolic) at week 26.

The FAS included all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS would contribute to the evaluation "as randomised". Missing data imputed from a mixed model for repeated measures with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit.

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

End point timeframe:

Week 0, Week 26

| End point values | Semaglutide 0.05 mg | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.3 mg |
|--------------------------------------|---------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 63 | 65 | 63 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic blood pressure | -5.74 (± 12.30) | -2.77 (± 13.21) | -4.25 (± 12.24) | -9.85 (± 11.58) |
| Diastolic blood pressure | -0.60 (± 8.78) | 0.66 (± 8.26) | -1.62 (± 9.38) | -4.02 (± 8.56) |

| End point values | Liraglutide 0.3 mg | Liraglutide 0.6 mg | Liraglutide 1.2 mg | Liraglutide 1.8 mg |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 64 | 64 | 64 | 65 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic blood pressure | -3.77 (± 9.79) | -3.20 (± 10.89) | -4.69 (± 12.73) | -2.99 (± 11.94) |
| Diastolic blood pressure | -1.77 (± 7.37) | -1.89 (± 8.20) | -0.60 (± 6.78) | 0.63 (± 8.13) |

| End point values | Placebo | Semaglutide flexible | | |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 129 | 64 | | |

| | | | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Systolic blood pressure | -2.34 (± 11.40) | -6.62 (± 14.02) | | |
| Diastolic blood pressure | -0.61 (± 8.50) | -1.69 (± 8.25) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to week 33.

Adverse event reporting additional description:

Safety analysis set (SAS) included all randomised subjects exposed to at least one dose of trial product. Subjects in the SAS would contribute to the evaluation "as treated". Treatment-emergent adverse events (TEAEs) were defined as events recorded from baseline and until completion of the post-treatment follow-up visit (7 weeks).

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Sema 0.05 mg |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|--------------|
| Reporting group title | Sema 0.10 mg |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|--------------|
| Reporting group title | Sema 0.20 mg |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|--------------|
| Reporting group title | Sema 0.30 mg |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|--------------|
| Reporting group title | Lira 0.30 mg |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|--------------|
| Reporting group title | Lira 0.60 mg |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|--------------|
| Reporting group title | Lira 1.20 mg |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|--------------|
| Reporting group title | Lira 1.80 mg |
|-----------------------|--------------|

Reporting group description: -

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

Reporting group description: -

| | |
|-----------------------|---------------|
| Reporting group title | Sema flexible |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | Sema 0.05 mg | Sema 0.10 mg | Sema 0.20 mg |
|---|-----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 3 / 63 (4.76%) | 2 / 65 (3.08%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Spinal meningioma benign | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Vascular disorders | | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Surgical and medical procedures | | | |
| Coronary revascularisation | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Endarterectomy | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Percutaneous coronary intervention | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Stent placement | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Vascular graft | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 oedema | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 | | | |
| Catheterisation cardiac | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystoscopy | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Myocardial infarction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 65 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Epiplonic appendagitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Infections and infestations | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 0 / 65 (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 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Pharyngitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 0 / 65 (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 | Sema 0.30 mg | Lira 0.30 mg | Lira 0.60 mg |
|--|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 63 (3.17%) | 1 / 64 (1.56%) | 2 / 64 (3.13%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Spinal meningioma benign subjects affected / exposed | 1 / 63 (1.59%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Vascular disorders | | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Surgical and medical procedures | | | |
| Coronary revascularisation | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Endarterectomy | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Percutaneous coronary intervention | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Stent placement | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Vascular graft | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 64 (1.56%) | 0 / 64 (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 |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 oedema | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 | | | |
| Catheterisation cardiac | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Cystoscopy | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 myocardial infarction | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 disease | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Ischaemic stroke | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 1 / 64 (1.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Epiplonic appendagitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Dupuytren's contracture | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Infections and infestations | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 64 (0.00%) | 0 / 64 (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 | Lira 1.20 mg | Lira 1.80 mg | Placebo |
|---|----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 7 / 65 (10.77%) | 4 / 129 (3.10%) |
| 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) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Spinal meningioma benign | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Vascular disorders | | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Coronary revascularisation | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Endarterectomy | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Percutaneous coronary intervention | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Stent placement | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Vascular graft | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |

| | | | |
|---|----------------|----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Investigations | | | |
| Catheterisation cardiac | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Cystoscopy | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 myocardial infarction | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 65 (1.54%) | 0 / 129 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 disease | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 65 (0.00%) | 0 / 129 (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 | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|----------------|-----------------|
| Anal fistula | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Epiplonic appendagitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Infections and infestations | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 |
| Gastroenteritis viral | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 65 (1.54%) | 0 / 129 (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 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 1 / 129 (0.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 65 (0.00%) | 0 / 129 (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 | Sema flexible | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 64 (6.25%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal meningioma benign | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Coronary revascularisation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endarterectomy | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Percutaneous coronary intervention | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stent placement | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Vascular graft | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Catheterisation cardiac | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystoscopy | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 64 (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 | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |

| | | | |
|---|----------------|--|--|
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epiploic appendagitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dupuytren's contracture | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 64 (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: 5 %

| Non-serious adverse events | Sema 0.05 mg | Sema 0.10 mg | Sema 0.20 mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 64 (50.00%) | 34 / 63 (53.97%) | 39 / 65 (60.00%) |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 3 / 63 (4.76%) | 3 / 65 (4.62%) |
| occurrences (all) | 3 | 3 | 3 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 4 / 63 (6.35%) | 2 / 65 (3.08%) |
| occurrences (all) | 2 | 4 | 2 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 4 / 63 (6.35%) | 2 / 65 (3.08%) |
| occurrences (all) | 4 | 6 | 2 |
| Headache | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 8 / 63 (12.70%) | 4 / 65 (6.15%) |
| occurrences (all) | 17 | 30 | 13 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 1 / 63 (1.59%) | 4 / 65 (6.15%) |
| occurrences (all) | 2 | 1 | 4 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 3 / 63 (4.76%) | 1 / 65 (1.54%) |
| occurrences (all) | 2 | 4 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 2 / 63 (3.17%) | 3 / 65 (4.62%) |
| occurrences (all) | 4 | 4 | 7 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 1 / 63 (1.59%) | 4 / 65 (6.15%) |
| occurrences (all) | 0 | 1 | 5 |
| Constipation | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 4 / 63 (6.35%) 4 | 6 / 65 (9.23%) 11 |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 64 (10.94%) 10 | 10 / 63 (15.87%) 13 | 10 / 65 (15.38%) 15 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 6 | 5 / 63 (7.94%) 7 | 5 / 65 (7.69%) 8 |
| Flatulence subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 1 / 63 (1.59%) 5 | 4 / 65 (6.15%) 6 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 4 / 63 (6.35%) 8 | 3 / 65 (4.62%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 11 / 64 (17.19%) 16 | 12 / 63 (19.05%) 20 | 14 / 65 (21.54%) 22 |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 10 | 4 / 63 (6.35%) 13 | 6 / 65 (9.23%) 9 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 63 (1.59%) 1 | 0 / 65 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 3 | 2 / 63 (3.17%) 2 | 0 / 65 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 63 (0.00%) 0 | 3 / 65 (4.62%) 3 |
| Back pain subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 4 / 63 (6.35%) 4 | 2 / 65 (3.08%) 2 |
| Muscle spasms | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 1 / 63 (1.59%) 1 | 0 / 65 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 6 / 63 (9.52%) | 4 / 65 (6.15%) |
| occurrences (all) | 12 | 7 | 4 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 63 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 2 / 63 (3.17%) | 1 / 65 (1.54%) |
| occurrences (all) | 8 | 2 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 7 / 63 (11.11%) | 6 / 65 (9.23%) |
| occurrences (all) | 3 | 7 | 6 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 63 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 1 | 0 | 1 |

| Non-serious adverse events | Sema 0.30 mg | Lira 0.30 mg | Lira 0.60 mg |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 63 (66.67%) | 35 / 64 (54.69%) | 28 / 64 (43.75%) |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 3 / 64 (4.69%) | 3 / 64 (4.69%) |
| occurrences (all) | 3 | 4 | 5 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 3 / 64 (4.69%) | 0 / 64 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|--|------------------|----------------|----------------|
| subjects affected / exposed | 3 / 63 (4.76%) | 0 / 64 (0.00%) | 3 / 64 (4.69%) |
| occurrences (all) | 4 | 0 | 4 |
| Headache | | | |
| subjects affected / exposed | 7 / 63 (11.11%) | 5 / 64 (7.81%) | 3 / 64 (4.69%) |
| occurrences (all) | 11 | 7 | 11 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 64 (0.00%) | 4 / 64 (6.25%) |
| occurrences (all) | 1 | 0 | 5 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 63 (3.17%) | 1 / 64 (1.56%) | 3 / 64 (4.69%) |
| occurrences (all) | 3 | 1 | 5 |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 63 (7.94%) | 3 / 64 (4.69%) | 0 / 64 (0.00%) |
| occurrences (all) | 6 | 3 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | 1 / 64 (1.56%) | 2 / 64 (3.13%) |
| occurrences (all) | 4 | 2 | 2 |
| Constipation | | | |
| subjects affected / exposed | 5 / 63 (7.94%) | 0 / 64 (0.00%) | 3 / 64 (4.69%) |
| occurrences (all) | 7 | 0 | 3 |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 63 (25.40%) | 5 / 64 (7.81%) | 5 / 64 (7.81%) |
| occurrences (all) | 29 | 5 | 9 |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 63 (9.52%) | 2 / 64 (3.13%) | 3 / 64 (4.69%) |
| occurrences (all) | 6 | 2 | 3 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 1 | 0 | 3 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 0 / 64 (0.00%) | 2 / 64 (3.13%) |
| occurrences (all) | 3 | 0 | 2 |
| Nausea | | | |

| | | | |
|---|------------------------|---------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 16 / 63 (25.40%) 22 | 6 / 64 (9.38%) 7 | 7 / 64 (10.94%) 11 |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 63 (9.52%) 8 | 1 / 64 (1.56%) 1 | 7 / 64 (10.94%) 10 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | 3 / 64 (4.69%) 4 | 4 / 64 (6.25%) 5 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | 2 / 64 (3.13%) 2 | 4 / 64 (6.25%) 4 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 4 | 1 / 64 (1.56%) 1 | 0 / 64 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 4 | 3 / 64 (4.69%) 3 | 2 / 64 (3.13%) 2 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 63 (0.00%) 0 | 0 / 64 (0.00%) 0 | 4 / 64 (6.25%) 4 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 1 / 64 (1.56%) 1 | 1 / 64 (1.56%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 6 | 4 / 64 (6.25%) 5 | 3 / 64 (4.69%) 3 |
| Sinusitis subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | 5 / 64 (7.81%) 5 | 2 / 64 (3.13%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 7 / 63 (11.11%) 7 | 6 / 64 (9.38%) 6 | 1 / 64 (1.56%) 1 |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 8 / 63 (12.70%) 8 | 2 / 64 (3.13%) 3 | 1 / 64 (1.56%) 1 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 63 (0.00%) 0 | 2 / 64 (3.13%) 3 | 3 / 64 (4.69%) 6 |

| Non-serious adverse events | Lira 1.20 mg | Lira 1.80 mg | Placebo |
|--|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 38 / 64 (59.38%) | 35 / 65 (53.85%) | 61 / 129 (47.29%) |
| Investigations Lipase increased subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 5 | 7 / 65 (10.77%) 7 | 4 / 129 (3.10%) 4 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 3 / 65 (4.62%) 3 | 3 / 129 (2.33%) 3 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 10 / 64 (15.63%) 16 | 4 / 65 (6.15%) 5 4 / 65 (6.15%) 8 | 3 / 129 (2.33%) 3 3 / 129 (2.33%) 3 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | 2 / 65 (3.08%) 2 | 3 / 129 (2.33%) 3 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper | 2 / 64 (3.13%) 2 4 / 64 (6.25%) 4 | 4 / 65 (6.15%) 13 0 / 65 (0.00%) 0 | 3 / 129 (2.33%) 4 1 / 129 (0.78%) 1 |

| | | | |
|---|-----------------|------------------|-------------------|
| subjects affected / exposed | 2 / 64 (3.13%) | 3 / 65 (4.62%) | 3 / 129 (2.33%) |
| occurrences (all) | 2 | 4 | 3 |
| Constipation | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 7 / 65 (10.77%) | 4 / 129 (3.10%) |
| occurrences (all) | 2 | 7 | 4 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 64 (7.81%) | 8 / 65 (12.31%) | 14 / 129 (10.85%) |
| occurrences (all) | 8 | 16 | 18 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 3 / 65 (4.62%) | 1 / 129 (0.78%) |
| occurrences (all) | 1 | 3 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 1 / 65 (1.54%) | 1 / 129 (0.78%) |
| occurrences (all) | 3 | 2 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 1 / 65 (1.54%) | 1 / 129 (0.78%) |
| occurrences (all) | 1 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 7 / 64 (10.94%) | 13 / 65 (20.00%) | 6 / 129 (4.65%) |
| occurrences (all) | 11 | 18 | 7 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 5 / 65 (7.69%) | 3 / 129 (2.33%) |
| occurrences (all) | 1 | 8 | 3 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 1 / 65 (1.54%) | 5 / 129 (3.88%) |
| occurrences (all) | 3 | 2 | 6 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 65 (0.00%) | 2 / 129 (1.55%) |
| occurrences (all) | 2 | 0 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 1 / 65 (1.54%) | 6 / 129 (4.65%) |
| occurrences (all) | 2 | 1 | 7 |
| Back pain | | | |

| | | | |
|---|---------------------|---------------------|------------------------|
| subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 4 / 65 (6.15%) 4 | 3 / 129 (2.33%) 3 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | 1 / 65 (1.54%) 1 | 2 / 129 (1.55%) 2 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 4 / 65 (6.15%) 4 | 3 / 129 (2.33%) 3 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 7 | 5 / 65 (7.69%) 6 | 7 / 129 (5.43%) 9 |
| Sinusitis subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 2 | 1 / 65 (1.54%) 1 | 2 / 129 (1.55%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 64 (3.13%) 3 | 5 / 65 (7.69%) 6 | 9 / 129 (6.98%) 11 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 3 / 65 (4.62%) 3 | 1 / 129 (0.78%) 1 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | 0 / 65 (0.00%) 0 | 11 / 129 (8.53%) 11 |

| | | | |
|--|---------------------|--|--|
| Non-serious adverse events | Sema flexible | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 44 / 64 (68.75%) | | |
| Investigations | | | |
| Lipase increased subjects affected / exposed occurrences (all) | 5 / 64 (7.81%) 5 | | |
| Vascular disorders | | | |
| Hypertension subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | | |

| | | | |
|--|---|--|--|
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 8 7 / 64 (10.94%) 14 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 | | |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 4 4 / 64 (6.25%) 7 6 / 64 (9.38%) 8 4 / 64 (6.25%) 6 11 / 64 (17.19%) 22 4 / 64 (6.25%) 4 6 / 64 (9.38%) 9 4 / 64 (6.25%) 5 | | |

| | | | |
|---|------------------------|--|--|
| Nausea subjects affected / exposed occurrences (all) | 25 / 64 (39.06%) 35 | | |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 64 (9.38%) 8 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 3 | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 3 / 64 (4.69%) 4 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 5 | | |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 1 / 64 (1.56%) 1 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 10 / 64 (15.63%) 11 | | |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 64 (0.00%) 0 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 64 (6.25%) 6 | | |

| | | | |
|------------------------------------|-----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 64 (14.06%) | | |
| occurrences (all) | 9 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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|----------------|
| Not applicable |
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Notes: