



Clinical trial results:

Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2016-000685-39 |
| Trial protocol | GB GR BG FI SE NL AT BE FR ES DK |
| Global end of trial date | 19 March 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 01 April 2021 |
| First version publication date | 01 April 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN9931-4296 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02970942 |
| WHO universal trial number (UTN) | U1111-1179-7464 |
| Other trial identifiers | Japanese registration number: 25-1634 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novo Nordisk A/S |
| Sponsor organisation address | Novo Allé, Bagsvaerd, Denmark, 2880 |
| Public contact | Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com |
| Scientific contact | Clinical Reporting Anchor and Disclosure (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 | 15 September 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 February 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the effect of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of non-alcoholic steatohepatitis (NASH).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Fortaleza, Brazil, 2013) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (June 1996), including archiving of essential documents, and 21 United States Code of Federal Regulations (CFR) 312.120.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 30 November 2016 |
| 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 | Australia: 4 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | Bulgaria: 15 |
| Country: Number of subjects enrolled | Canada: 25 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Spain: 12 |
| Country: Number of subjects enrolled | Finland: 2 |
| Country: Number of subjects enrolled | France: 17 |
| Country: Number of subjects enrolled | United Kingdom: 28 |
| Country: Number of subjects enrolled | Greece: 12 |
| Country: Number of subjects enrolled | Japan: 41 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Russian Federation: 49 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | United States: 91 |
| Worldwide total number of subjects | 320 |
| EEA total number of subjects | 82 |

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) | 262 |
| From 65 to 84 years | 58 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Trial was conducted at 114 sites in 16 countries (number of sites that screened subjects/randomised subjects): Australia(4/3); Austria(3/3); Belgium(4/4); Bulgaria(2/2); Canada(9/7); Denmark(2/2); Finland(1/1); France(8/6); Greece(5/5); Japan(13/12); Netherlands(7/5); Russian Federation(25/17); Spain(6/5); Sweden(3/2); United

Pre-assignment

Screening details:

Subjects were randomised in a 3:3:3:1:1:1 ratio to receive once-daily semaglutide or placebo subcutaneously. After randomisation, the subjects entered a dose-escalation period, with increase in dose every 4 weeks until the target dose was reached.

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 | Investigator, Subject |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Semaglutide 0.1 mg |

Arm description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B 1 mg/ml NovoPen4 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).

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

Arm description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B 1 mg/ml NovoPen4 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).

| | |
|---|--------------------------------|
| Arm title | Semaglutide 0.4 mg |
| Arm description: Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72). | |
| Arm type | Experimental |
| Investigational medicinal product name | Semaglutide B 1 mg/ml NovoPen4 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).

| | |
|--|------------------------|
| Arm title | Placebo |
| Arm description: Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks. | |
| Arm type | Placebo |
| Investigational medicinal product name | Semaglutide placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks.

| Number of subjects in period 1 | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg |
|---------------------------------------|--------------------|--------------------|--------------------|
| Started | 80 | 78 | 82 |
| Completed | 76 | 72 | 77 |
| Not completed | 4 | 6 | 5 |
| Death | - | 1 | - |
| Withdrawal by Subject | 3 | 5 | 3 |
| Lost to follow-up | 1 | - | 2 |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 80 |
| Completed | 77 |
| Not completed | 3 |
| Death | - |
| Withdrawal by Subject | 2 |
| Lost to follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------|
| Reporting group title | Semaglutide 0.1 mg |
| Reporting group description: | |
| Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72). | |
| Reporting group title | Semaglutide 0.2 mg |
| Reporting group description: | |
| Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72). | |
| Reporting group title | Semaglutide 0.4 mg |
| Reporting group description: | |
| Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72). | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks. | |

| Reporting group values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg |
|------------------------|--------------------|--------------------|--------------------|
| Number of subjects | 80 | 78 | 82 |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|--------|-------|--------|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.2 | 58.1 | 54.3 |
| standard deviation | ± 10.9 | ± 9.9 | ± 10.2 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 51 | 52 | 47 |
| Male | 29 | 26 | 35 |

| Reporting group values | Placebo | Total | |
|------------------------|---------|-------|--|
| Number of subjects | 80 | 320 | |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|--------|-----|--|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 52.4 | | |
| standard deviation | ± 10.8 | - | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 44 | 194 | |

| | | | |
|------|----|-----|--|
| Male | 36 | 126 | |
|------|----|-----|--|

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Semaglutide 0.1 mg |
| Reporting group description: Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72). | |
| Reporting group title | Semaglutide 0.2 mg |
| Reporting group description: Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72). | |
| Reporting group title | Semaglutide 0.4 mg |
| Reporting group description: Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72). | |
| Reporting group title | Placebo |
| Reporting group description: Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks. | |

Primary: NASH resolution without worsening of fibrosis (yes/no)

| | |
|--|--|
| End point title | NASH resolution without worsening of fibrosis (yes/no) |
| End point description: NASH resolution defined as lobular inflammation of 0 or 1; hepatocellular ballooning reduced to 0; both criteria were necessary conditions. Hepatocellular ballooning range 0-2; lobular inflammation ranges from 0-3, with higher scores indicating more severe hepatocellular ballooning or lobular inflammation. Worsening of fibrosis defined by an increase in fibrosis at least one stage of Kleiner fibrosis classification: fibrosis stages range 0-4, with higher scores indicating greater fibrosis (0=None,4=Cirrhosis). Full analysis set included all randomised subjects. Number of subjects analysed = Number of subjects with fibrosis stage 2 or 3 at baseline who contributed to the analysis. In below table, 'Yes' infers percentage of subjects who achieved NASH resolution without worsening of fibrosis and 'No' infers vice-versa; 'Missing' refers to percentage of subjects with data missing due to different reasons (lost to follow-up, withdrawal). | |
| End point type | Primary |
| End point timeframe: After 72 weeks | |

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|-------------------------------|--------------------|--------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 59 | 56 | 58 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Yes | 40.4 | 35.6 | 58.9 | 17.2 |
| No | 54.4 | 47.5 | 30.4 | 74.1 |
| Missing | 5.3 | 16.9 | 10.7 | 8.6 |

Statistical analyses

| | |
|--|-----------------------------------|
| Statistical analysis title | Semaglutide 0.1 mg versus Placebo |
| Statistical analysis description: The common odds ratio was estimated together with 95% confidence interval using the Mantel-Haenszel estimator associated with the Cochran-Mantel-Haenszel test. | |
| Comparison groups | Semaglutide 0.1 mg v Placebo |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | t-test, 2-sided |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.29 |
| upper limit | 8.86 |

| | |
|--|-----------------------------------|
| Statistical analysis title | Semaglutide 0.2 mg versus Placebo |
| Statistical analysis description: The common odds ratio was estimated together with 95% confidence interval using the Mantel-Haenszel estimator associated with the Cochran-Mantel-Haenszel test. | |
| Comparison groups | Semaglutide 0.2 mg v Placebo |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0359 |
| Method | t-test, 2-sided |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 7.56 |

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Semaglutide 0.4 mg versus Placebo |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

The common odds ratio was estimated together with 95% confidence interval using the Mantel-Haenszel

estimator associated with the Cochran-Mantel-Haenszel test.

| | |
|---|------------------------------|
| Comparison groups | Semaglutide 0.4 mg v Placebo |
| Number of subjects included in analysis | 114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | t-test, 2-sided |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 6.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.6 |
| upper limit | 17.63 |

Secondary: At least one stage of liver fibrosis improvement with no worsening of NASH (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH clinical research network (CRN) criteria)

| | |
|-----------------|---|
| End point title | At least one stage of liver fibrosis improvement with no worsening of NASH (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH clinical research network (CRN) criteria) |
|-----------------|---|

End point description:

Worsening of fibrosis defined by an increase in fibrosis at least one stage of Kleiner fibrosis classification: fibrosis stages range from 0-4, higher scores indicate greater fibrosis (0=None, 4=Cirrhosis). Full analysis set included all randomised subjects. Number of subjects analysed = Number of subjects with fibrosis stage 2 or 3 at baseline who contributed to the analysis. In below table, 'Yes' infers percentage of subjects who achieved at least one stage of fibrosis improvement with no worsening of NASH; 'No' infers vice-versa; 'Missing' refers to percentage of subjects with data missing due to different reasons (lost to follow-up, withdrawal).

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

End point timeframe:

After 72 weeks

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|-------------------------------|--------------------|--------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 57 | 59 | 56 | 58 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Yes | 49.1 | 32.2 | 42.9 | 32.8 |
| No | 45.6 | 50.8 | 46.4 | 58.6 |
| Missing | 5.3 | 16.9 | 10.7 | 8.6 |

Statistical analyses

Secondary: Change in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) (0-8)

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|-----------------|--|
| End point title | Change in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) (0-8) |
|-----------------|--|

End point description:

Percentage of subjects who had worsened, improved or had no change in total NAS from baseline to week 72 is presented. Worsening is defined as an increase of at least 1 in the NAS; Improvement is defined as a decrease of at least 1 in the NAS; while no change corresponds to no change in NAS from baseline to week 72. NAS is calculated as the sum of scores for steatosis (0 to 3), lobular inflammation (0 to 3), and hepatocyte ballooning (0 to 2). Therefore, it is assessed on a scale of 0-8, with higher scores indicating more severe disease. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects.

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

End point timeframe:

From baseline to week 72

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|-------------------------------|-----------------------|-----------------------|-----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 78 | 82 | 80 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Improvement | 71.3 | 79.5 | 82.9 | 43.8 |
| Worsening | 7.5 | 2.6 | 3.7 | 16.3 |
| No change | 13.8 | 5.1 | 1.2 | 27.5 |
| Missing | 7.5 | 12.8 | 12.2 | 12.5 |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in stage of fibrosis according to the Kleiner fibrosis classification (0-4)

| | |
|-----------------|--|
| End point title | Change in stage of fibrosis according to the Kleiner fibrosis classification (0-4) |
|-----------------|--|

End point description:

Percentage of subjects who had improved, worsened, or had no change in fibrosis stage from baseline to week 72 is presented. The degree of fibrosis is described by the Kleiner fibrosis staging system, ranging from F0 (absence of fibrosis), F1 (portal/perisinusoidal fibrosis), F2 (perisinusoidal and portal/periportal fibrosis), F3 (septal or bridging fibrosis) through F4 (cirrhosis). The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects.

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

End point timeframe:

From baseline to week 72

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|-------------------------------|-----------------------|-----------------------|-----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 78 | 82 | 80 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Improvement | 46.3 | 32.1 | 42.7 | 31.3 |
| Worsening | 10.0 | 7.7 | 4.9 | 18.8 |
| No change | 36.3 | 42.3 | 36.6 | 37.5 |
| Missing | 7.5 | 17.9 | 15.9 | 12.5 |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in activity component of steatosis-activity-fibrosis (SAF) score (0-4)

| | |
|-----------------|---|
| End point title | Change in activity component of steatosis-activity-fibrosis (SAF) score (0-4) |
|-----------------|---|

End point description:

Percentage of subjects who had improved, worsened, or had no change in the activity component of the SAF score from baseline to week 72 is presented. The activity component of the SAF score is defined as the unweighted sum of hepatocyte ballooning (0 to 2) and lobular inflammation (0 to 3). The definition of the lobular inflammation score is modified in this calculation so that the scores 2 and 3 on the original scale are merged to a score 2. The possible range of the sum is thus 0 to 4. For all scores, a higher value indicates a more severe state of disease. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects.

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

End point timeframe:

From baseline to week 72

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|-------------------------------|-----------------------|-----------------------|-----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 80 | 78 | 82 | 80 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Improvement | 62.5 | 71.8 | 72.0 | 42.5 |
| Worsening | 7.5 | 3.8 | 1.2 | 11.3 |
| No change | 22.5 | 11.5 | 14.6 | 33.8 |
| Missing | 7.5 | 12.8 | 12.2 | 12.5 |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

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|-----------------|--|
| End point title | Change in fasting plasma glucose (FPG) |
|-----------------|--|

End point description:

Change in FPG from baseline to week 72 is presented. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects. Number of subjects analyzed = Number of subjects with type 2 diabetes who contributed to the analysis.

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

End point timeframe:

From baseline to week 72

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|--------------------------------------|-----------------------|-----------------------|-----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 45 | 44 | 47 | 48 |
| Units: Millimoles per liter | | | | |
| arithmetic mean (standard deviation) | -1.39 (± 2.53) | -2.17 (± 1.82) | -2.09 (± 2.68) | -0.34 (± 2.72) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in glycosylated haemoglobin A1c (HbA1c)

| | |
|-----------------|--|
| End point title | Change in glycosylated haemoglobin A1c (HbA1c) |
|-----------------|--|

End point description:

Change in HbA1c from baseline to week 72 is presented. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects. Number of subjects analyzed = Number of subjects with type 2 diabetes who contributed to the analysis.

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

End point timeframe:

From baseline to week 72

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|--------------------------------------|-----------------------|-----------------------|-----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 46 | 45 | 47 | 47 |
| Units: Percentage point of HbA1c | | | | |
| arithmetic mean (standard deviation) | -0.7 (± 1.1) | -1.2 (± 0.9) | -1.2 (± 1.0) | -0.0 (± 1.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in serum enhanced liver fibrosis (ELF)

| | |
|--|---|
| End point title | Change in serum enhanced liver fibrosis (ELF) |
| End point description: | |
| Change in ELF from baseline to week 72 is presented. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects. Number of subjects analyzed = Number of subjects who contributed to the analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to week 72 | |

| End point values | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg | Placebo |
|--------------------------------------|-----------------------|-----------------------|-----------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 76 | 70 | 76 | 75 |
| Units: Change in ELF score | | | | |
| arithmetic mean (standard deviation) | -0.4 (± 0.7) | -0.4 (± 0.8) | -0.6 (± 0.8) | 0.1 (± 0.7) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From week 0 to week 79

Results are based on safety analysis set which included all subjects who received at least one dose of randomised treatment. All adverse events reported here are treatment emergent adverse events (TEAEs).

Adverse event reporting additional description:

TEAE was defined as an event that had onset date during on-treatment period (for AEs), which started from date of first administration of trial product and ended on date of whatever came first: 1) last dose of trial product + 49 days (7 half lives of semaglutide); 2) end of the in-trial period.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Semaglutide 0.1 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).

| | |
|-----------------------|--------------------|
| Reporting group title | Semaglutide 0.2 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).

| | |
|-----------------------|--------------------|
| Reporting group title | Semaglutide 0.4 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).

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

Reporting group description:

Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks.

| Serious adverse events | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 80 (15.00%) | 15 / 78 (19.23%) | 12 / 81 (14.81%) |
| 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) | | | |
| Cholesteatoma | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Neurilemmoma benign | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Peripheral T-cell lymphoma unspecified | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 leiomyoma | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Immune system disorders | | | |
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Reproductive system and breast disorders | | | |
| Dysfunctional uterine bleeding | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Major depression | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 0 / 81 (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 | | | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Transient epileptic amnesia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ischaemic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Constipation | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Gastrointestinal polyp haemorrhage | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Megacolon | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 78 (1.28%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 2 / 78 (2.56%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 0 / 81 (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 | | | |
| Basedow's disease | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| 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 pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Cystitis escherichia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (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 | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis E | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| 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 | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | 0 / 78 (0.00%) | 0 / 81 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 78 (1.28%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 0 / 81 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 80 (10.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cholesteatoma | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neurilemmoma benign | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral T-cell lymphoma unspecified | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Reproductive system and breast disorders | | | |
| Dysfunctional uterine bleeding | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Major depression | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient epileptic amnesia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ischaemic | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulum intestinal haemorrhagic | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal polyp haemorrhage | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Megacolon | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Basedow's disease | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot deformity | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis escherichia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis E | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 80 (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 | Semaglutide 0.1 mg | Semaglutide 0.2 mg | Semaglutide 0.4 mg |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 61 / 80 (76.25%) | 64 / 78 (82.05%) | 63 / 81 (77.78%) |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 7 / 78 (8.97%) | 1 / 81 (1.23%) |
| occurrences (all) | 5 | 8 | 3 |
| Injury, poisoning and procedural | | | |

| | | | |
|--|-----------------|------------------|------------------|
| complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 2 / 78 (2.56%) | 2 / 81 (2.47%) |
| occurrences (all) | 7 | 2 | 2 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 3 / 78 (3.85%) | 3 / 81 (3.70%) |
| occurrences (all) | 3 | 3 | 3 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | 6 / 78 (7.69%) | 8 / 81 (9.88%) |
| occurrences (all) | 8 | 8 | 10 |
| Headache | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 10 / 78 (12.82%) | 10 / 81 (12.35%) |
| occurrences (all) | 11 | 13 | 13 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | 8 / 78 (10.26%) | 7 / 81 (8.64%) |
| occurrences (all) | 7 | 8 | 8 |
| Injection site bruising | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 5 / 78 (6.41%) | 3 / 81 (3.70%) |
| occurrences (all) | 1 | 10 | 4 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 4 / 78 (5.13%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 4 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 8 / 78 (10.26%) | 4 / 81 (4.94%) |
| occurrences (all) | 1 | 9 | 7 |
| Abdominal pain | | | |
| subjects affected / exposed | 9 / 80 (11.25%) | 8 / 78 (10.26%) | 6 / 81 (7.41%) |
| occurrences (all) | 10 | 9 | 7 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 6 / 78 (7.69%) | 8 / 81 (9.88%) |
| occurrences (all) | 5 | 7 | 10 |
| Constipation | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 12 / 80 (15.00%) | 17 / 78 (21.79%) | 18 / 81 (22.22%) |
| occurrences (all) | 14 | 22 | 20 |
| Diarrhoea | | | |
| subjects affected / exposed | 23 / 80 (28.75%) | 22 / 78 (28.21%) | 16 / 81 (19.75%) |
| occurrences (all) | 31 | 30 | 21 |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | 9 / 78 (11.54%) | 4 / 81 (4.94%) |
| occurrences (all) | 4 | 11 | 5 |
| Eructation | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | 6 / 78 (7.69%) | 1 / 81 (1.23%) |
| occurrences (all) | 6 | 6 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | 5 / 78 (6.41%) | 3 / 81 (3.70%) |
| occurrences (all) | 2 | 5 | 3 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | 4 / 78 (5.13%) | 5 / 81 (6.17%) |
| occurrences (all) | 3 | 5 | 6 |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 4 / 78 (5.13%) | 3 / 81 (3.70%) |
| occurrences (all) | 1 | 4 | 3 |
| Nausea | | | |
| subjects affected / exposed | 24 / 80 (30.00%) | 29 / 78 (37.18%) | 33 / 81 (40.74%) |
| occurrences (all) | 32 | 39 | 49 |
| Vomiting | | | |
| subjects affected / exposed | 14 / 80 (17.50%) | 17 / 78 (21.79%) | 12 / 81 (14.81%) |
| occurrences (all) | 21 | 26 | 29 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 0 / 78 (0.00%) | 1 / 81 (1.23%) |
| occurrences (all) | 1 | 0 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 1 / 78 (1.28%) | 4 / 81 (4.94%) |
| occurrences (all) | 1 | 1 | 5 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | 4 / 78 (5.13%) 4 | 8 / 81 (9.88%) 8 |
| Back pain subjects affected / exposed occurrences (all) | 7 / 80 (8.75%) 10 | 5 / 78 (6.41%) 5 | 10 / 81 (12.35%) 10 |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 1 / 78 (1.28%) 1 | 3 / 81 (3.70%) 3 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | 1 / 78 (1.28%) 1 | 2 / 81 (2.47%) 2 |
| Infections and infestations | | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 2 / 78 (2.56%) 2 | 1 / 81 (1.23%) 1 |
| Influenza subjects affected / exposed occurrences (all) | 7 / 80 (8.75%) 7 | 1 / 78 (1.28%) 1 | 3 / 81 (3.70%) 4 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 11 / 80 (13.75%) 15 | 15 / 78 (19.23%) 21 | 10 / 81 (12.35%) 11 |
| Sinusitis subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 7 / 78 (8.97%) 8 | 2 / 81 (2.47%) 4 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | 6 / 78 (7.69%) 8 | 3 / 81 (3.70%) 4 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 80 (6.25%) 7 | 2 / 78 (2.56%) 2 | 7 / 81 (8.64%) 9 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 16 / 80 (20.00%) 18 | 18 / 78 (23.08%) 18 | 18 / 81 (22.22%) 22 |
| Diabetes mellitus | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 80 (0.00%) | 1 / 78 (1.28%) | 0 / 81 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 80 (1.25%) | 2 / 78 (2.56%) | 3 / 81 (3.70%) |
| occurrences (all) | 1 | 3 | 6 |

| Non-serious adverse events | Placebo | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 80 (68.75%) | | |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | | |
| occurrences (all) | 2 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | | |
| occurrences (all) | 4 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 80 (7.50%) | | |
| occurrences (all) | 7 | | |
| Headache | | | |
| subjects affected / exposed | 8 / 80 (10.00%) | | |
| occurrences (all) | 10 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 7 / 80 (8.75%) | | |
| occurrences (all) | 7 | | |
| Injection site bruising | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | | |
| occurrences (all) | 2 | | |
| Pyrexia | | | |

| | | | |
|----------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 80 (1.25%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 4 / 80 (5.00%) | | |
| occurrences (all) | 5 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | | |
| occurrences (all) | 4 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 80 (3.75%) | | |
| occurrences (all) | 4 | | |
| Constipation | | | |
| subjects affected / exposed | 10 / 80 (12.50%) | | |
| occurrences (all) | 11 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 80 (13.75%) | | |
| occurrences (all) | 16 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 80 (6.25%) | | |
| occurrences (all) | 7 | | |
| Eructation | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences (all) | 0 | | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 80 (2.50%) | | |
| occurrences (all) | 2 | | |
| Large intestine polyp | | | |
| subjects affected / exposed | 0 / 80 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 9 / 80 (11.25%) | | |
| occurrences (all) | 10 | | |

| | | | |
|--|--|--|--|
| Vomiting subjects affected / exposed occurrences (all) | 2 / 80 (2.50%) 3 | | |
| Respiratory, thoracic and mediastinal disorders Respiratory disorder subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 5 | | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 5 / 80 (6.25%) 5 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 7 / 80 (8.75%) 7 6 / 80 (7.50%) 6 4 / 80 (5.00%) 4 5 / 80 (6.25%) 7 | | |
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis | 2 / 80 (2.50%) 2 6 / 80 (7.50%) 6 12 / 80 (15.00%) 22 | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 80 (1.25%) 1 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 5 / 80 (6.25%) 6 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 80 (0.00%) 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 4 | | |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 4 / 80 (5.00%) 5 | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 7 / 80 (8.75%) 8 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 13 September 2016 | The following changes were made as per this amendment: -Clarification of process for handling increased levels of liver blood parameters -Clarification that exclusion criterion 20 (retinopathy) is only applicable to subjects with type 2 diabetes (T2D) -Additional section added: Fundoscopy/fundus photography -Exclusion criterion for severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 milliliter per minute per meter square (mL/min/m2)) added, and continuous eGFR measurements during the trial |
| 29 December 2016 | The following changes were made as per this amendment: -Subjects developing T2D during the trial can be treated with antidiabetic medication -Exclusion criterion 8 updated: vitamin E and pioglitazone treatment must be stable for 90 days prior to screening/baseline liver biopsy -Statistical section updated: supportive analysis of the primary endpoint without pooling the placebo arms added. A sensitivity analysis of the primary endpoint where vitamin E use is included as a factor in the model, and a subgroup analysis for subjects who use vitamin E versus subjects who do not use vitamin E, added -Collection of daily dose for treatment with vitamin E and pioglitazone included -Text regarding new identified risk (retinopathy) included in risk/benefit section |
| 26 May 2017 | The following changes were made as per this amendment: -Changes to eligibility criteria implemented: Inclusion criteria 1 and 5, exclusion criteria 5, 6, 10, and 15 amended; Exclusion criteria 12 and 16 deleted -As a consequence of amending exclusion criterion 10 a new section with guidance on treatment of subjects with poorly controlled glycaemia included -Optional pre-screening included (blood samples and imaging (not involving radiation)) -Footnote to primary endpoint updated to clarify definition of resolution of NASH -Screen failure rate updated to 65% -Restrictions on bolus insulin treatment removed and short-term systemic use (less than or equal to (\leq) 14 days) of corticosteroids allowed -Visit 10 must be attended in a fasting state (for calcitonin measurement) |
| 02 October 2017 | The following changes were made as per this amendment: -Global sample size reduction: from 372 to 288 randomised subjects -Expected time for planned duration of recruitment period increased from 78 to 103 weeks -Inclusion of subjects with fibrosis stage 1 (inclusion criterion 7 has been updated) -Re-test of INR allowed (if screening albumin is within central laboratory reference range) -Rephrased exclusion criterion 9 regarding treatment with drugs with potential effect on steatosis |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported