



Clinical trial results:

Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin alone or basal insulin in combination with metformin in subjects with type 2 diabetes

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-004502-26 |
| Trial protocol | DE SK |
| Global end of trial date | 21 November 2015 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 03 December 2016 |
| First version publication date | 03 December 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NN9535-3627 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02305381 |
| WHO universal trial number (UTN) | U1111-1149-3738 |
| Other trial identifiers | Japanese trial registration: JapicCTI-142729 |

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 | 29 June 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate superiority of once-weekly dosing of two dose levels (0.5 mg and 1.0 mg) of semaglutide versus placebo on glycaemic control in subjects with type 2 diabetes (T2D) on basal insulin.

Protection of trial subjects:

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

Background therapy:

Subjects were to continue pre-trial background medication throughout the entire trial. Basal insulin with or without metformin were considered background medication.

Evidence for comparator:

Not applicable

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Germany: 70 |
| Country: Number of subjects enrolled | Japan: 61 |
| Country: Number of subjects enrolled | Serbia: 45 |
| Country: Number of subjects enrolled | Slovakia: 40 |
| Country: Number of subjects enrolled | United States: 180 |
| Worldwide total number of subjects | 396 |
| EEA total number of subjects | 110 |

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) | 281 |
| From 65 to 84 years | 114 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 90 sites in 5 countries, as follows: Germany: 10 sites; Japan: 6 sites; Serbia: 4 sites; Slovakia: 5 sites; United States: 65.

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 | Investigator, Subject |

Blinding implementation details:

Semaglutide and placebo were supplied in similar 1.5 mL pre-filled PDS290 pen-injector and were by all means visually identical and were packed and labelled to fulfil the requirements for double-blind procedures. Furthermore, equal volumes of semaglutide and placebo were administered during treatment ensuring blinding within dose-level.

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Semaglutide 0.5 mg |

Arm description:

Subjects received semaglutide 0.25 mg subcutaneous (sc) injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30.

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

Dosage and administration details:

Semaglutide injection was administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections were to be administered on the same day of the week during the trial.

| | |
|------------------|--------------------|
| Arm title | Semaglutide 1.0 mg |
|------------------|--------------------|

Arm description:

Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30.

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

Dosage and administration details:

Semaglutide injection was administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections were to be administered on the same day of the week during the trial.

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

Arm description:

Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 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:

Placebo injection was administered in the thigh, abdomen or upper arm, at any time of day irrespective of meals. The injections were to be administered on the same day of the week during the trial.

| Number of subjects in period 1 | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo |
|--|--------------------|--------------------|-------------------|
| Started | 132 | 131 | 133 |
| Premature discontinuation of treatment | 14 ^[1] | 16 ^[2] | 13 ^[3] |
| Completed | 127 | 127 | 126 |
| Not completed | 5 | 4 | 7 |
| Not completed | 5 | 4 | 7 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number represents only those participants who prematurely discontinued the treatment. However, subjects who prematurely discontinued treatment were allowed to continue participation in the trial.

Baseline characteristics

Reporting groups

| | |
|---|--------------------|
| Reporting group title | Semaglutide 0.5 mg |
| Reporting group description: Subjects received semaglutide 0.25 mg subcutaneous (sc) injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30. | |
| Reporting group title | Semaglutide 1.0 mg |
| Reporting group description: Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 weeks. | |

| Reporting group values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo |
|---|--------------------|--------------------|-----------|
| Number of subjects | 132 | 131 | 133 |
| Age Categorical Units: Subjects | | | |
| Adults (18-64 years) | 93 | 102 | 86 |
| From 65-84 years | 39 | 29 | 46 |
| 85 years and over | 0 | 0 | 1 |
| Age Continuous Units: years | | | |
| arithmetic mean | 59.1 | 58.5 | 58.8 |
| standard deviation | ± 10.3 | ± 9 | ± 10.9 |
| Gender Categorical Units: Subjects | | | |
| Female | 58 | 54 | 62 |
| Male | 74 | 77 | 71 |
| Glycosylated haemoglobin Units: percentage of glycosylated haemoglobin | | | |
| arithmetic mean | 8.36 | 8.31 | 8.42 |
| standard deviation | ± 0.83 | ± 0.82 | ± 0.88 |
| Body weight Units: kg | | | |
| arithmetic mean | 92.74 | 92.49 | 89.88 |
| standard deviation | ± 19.57 | ± 22.23 | ± 21.06 |
| Fasting plasma glucose Units: mg/dL | | | |
| arithmetic mean | 161 | 152.5 | 154.1 |
| standard deviation | ± 62.38 | ± 50.91 | ± 46.66 |
| Insulin Dose | | | |
| Number of subjects analysed for this parameter=131, 131 and 133 | | | |
| Units: international unit | | | |
| median | 35 | 36 | 36 |
| full range (min-max) | 15 to 300 | 14 to 320 | 12 to 124 |
| Diastolic Blood Pressure Units: mm Hg | | | |

| | | | |
|--|--------|---------|---------|
| arithmetic mean | 78.89 | 78.73 | 79.35 |
| standard deviation | ± 9.72 | ± 9.98 | ± 9.71 |
| Systolic Blood Pressure | | | |
| Units: mm Hg | | | |
| arithmetic mean | 134.87 | 134.4 | 134.99 |
| standard deviation | ± 15 | ± 16.32 | ± 16.68 |
| Diabetes Treatment Satisfaction Questionnaire | | | |
| The DTSQs questionnaire was used to assess subjects' treatment satisfaction and contained 8 components and evaluates the diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings towards the treatment. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Response options range from 6 (best case) to 0 (worst case). Total scores for treatment satisfaction range from 0-36. Higher scores indicate higher satisfaction. | | | |
| Units: scores on a scale | | | |
| arithmetic mean | 28.86 | 28.62 | 27.54 |
| standard deviation | ± 6.35 | ± 6.45 | ± 6.55 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 396 | | |
| Age Categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 281 | | |
| From 65-84 years | 114 | | |
| 85 years and over | 1 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 174 | | |
| Male | 222 | | |
| Glycosylated haemoglobin | | | |
| Units: percentage of glycosylated haemoglobin | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Body weight | | | |
| Units: kg | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Fasting plasma glucose | | | |
| Units: mg/dL | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Insulin Dose | | | |
| Number of subjects analysed for this parameter=131, 131 and 133 | | | |
| Units: international unit | | | |
| median | - | | |
| full range (min-max) | - | | |
| Diastolic Blood Pressure | | | |
| Units: mm Hg | | | |
| arithmetic mean | | | |

| | | | |
|--|---|--|--|
| standard deviation | - | | |
| Systolic Blood Pressure | | | |
| Units: mm Hg | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Diabetes Treatment Satisfaction Questionnaire | | | |
| The DTSQs questionnaire was used to assess subjects' treatment satisfaction and contained 8 components and evaluates the diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings towards the treatment. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Response options range from 6 (best case) to 0 (worst case). Total scores for treatment satisfaction range from 0-36. Higher scores indicate higher satisfaction. | | | |
| Units: scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Semaglutide 0.5 mg |
| Reporting group description: Subjects received semaglutide 0.25 mg subcutaneous (sc) injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30. | |
| Reporting group title | Semaglutide 1.0 mg |
| Reporting group description: Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 weeks. | |

Primary: Change in HbA1c

| | |
|---|-----------------|
| End point title | Change in HbA1c |
| End point description: Estimated mean change from baseline in HbA1c at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Analysis was performed on full analysis set which included all randomised subjects who had received at least 1 dose of randomised semaglutide or placebo. | |
| End point type | Primary |
| End point timeframe: From baseline to week 30 | |

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|--|----------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: percentage of glycosylated hemoglobin | | | | |
| least squares mean (standard error) | -1.45 (± 0.09) | -1.85 (± 0.09) | -0.09 (± 0.09) | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Analysis 1: Semaglutide 1.0 mg vs Placebo |
| Statistical analysis description: Hierarchical testing was performed as per sequence listed below: Change in HbA1c: semaglutide 1.0 mg vs placebo. Change in HbA1c: semaglutide 0.5 mg vs placebo. Change in body weight: semaglutide 1.0 mg vs placebo. Change in body weight: semaglutide 0.5 mg vs placebo. Analysis was performed using MMRM with treatment, country and stratification variable (HbA1c at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate | |

| | |
|---|------------------------------|
| Comparison groups | Semaglutide 1.0 mg v Placebo |
| Number of subjects included in analysis | 264 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.01 |
| upper limit | -1.5 |

Notes:

[1] - Superiority for change in HbA1c was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0%

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis 2: Semaglutide 1.0 mg vs Placebo |
|-----------------------------------|---|

Statistical analysis description:

Hierarchical testing was performed as per sequence listed below: Change in HbA1c: semaglutide 1.0 mg vs placebo. Change in HbA1c: semaglutide 0.5 mg vs placebo. Change in body weight: semaglutide 1.0 mg vs placebo. Change in body weight: semaglutide 0.5 mg vs placebo. Analysis was performed using MMRM with treatment, country and stratification variable (HbA1c at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate

| | |
|---|------------------------------|
| Comparison groups | Semaglutide 0.5 mg v Placebo |
| Number of subjects included in analysis | 265 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Treatment difference |
| Point estimate | -1.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.61 |
| upper limit | -1.1 |

Notes:

[2] - Superiority for change in HbA1c was claimed if the upper limit of the 2-sided 95% CI for the estimated difference was below 0%.

Secondary: Change in body weight

| | |
|-----------------|-----------------------|
| End point title | Change in body weight |
|-----------------|-----------------------|

End point description:

Estimated mean change from baseline in HbA1c at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Analysis was performed on full analysis set.

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

End point timeframe:

From baseline to week 30

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|-------------------------------------|-----------------------|-----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: kg | | | | |
| least squares mean (standard error) | -3.67 (± 0.36) | -6.42 (± 0.36) | -1.36 (± 0.37) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

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

End point description:

Estimated mean change from baseline in FPG at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Estimated mean change from baseline in FPG at week 30. Analysis was performed on full analysis set.

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

End point timeframe:

From baseline to week 30

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|-------------------------------------|-----------------------|-----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: mg/dL | | | | |
| least squares mean (standard error) | -29.14 (± 3.74) | -42.38 (± 3.76) | -8.51 (± 4.02) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in insulin dose

| | |
|-----------------|------------------------|
| End point title | Change in insulin dose |
|-----------------|------------------------|

End point description:

Estimated mean change from baseline in insulin dose at week 30 was measured in terms of ratio to baseline. Responses at week 30 are analysed using an Analysis of covariance model with treatment, country and stratification variable (HbA1c level at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of

metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using last observation carried forward. Analysis was performed on full analysis set.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From baseline to week 30 | |

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|-------------------------------------|-----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: ratio | | | | |
| least squares mean (standard error) | 0.9 (\pm 0.01) | 0.85 (\pm 0.01) | 0.96 (\pm 0.01) | |

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: | |
| Estimated mean change from baseline in systolic and diastolic blood pressure at week 30. The post-baseline responses are analysed using a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [\leq 8.0% or $>$ 8.0%] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using mixed model for repeated measurements. Analysis was performed on full analysis set. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to week 30 | |

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|-------------------------------------|-----------------------|-----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: mm Hg | | | | |
| least squares mean (standard error) | | | | |
| Diastolic blood pressure | -1.84 (\pm 0.73) | -1.5 (\pm 0.74) | -2.17 (\pm 0.79) | |
| Systolic blood pressure | -4.29 (\pm 1.26) | -7.27 (\pm 1.27) | -0.99 (\pm 1.34) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in patient reported outcomes, Diabetes Treatment Satisfaction Questionnaire (DTSQ)

| | |
|-----------------|---|
| End point title | Change in patient reported outcomes, Diabetes Treatment Satisfaction Questionnaire (DTSQ) |
|-----------------|---|

End point description:

The DTSQs questionnaire was used to assess subjects' treatment satisfaction and contained 8 components and evaluates the diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings towards the treatment. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Response options range from 6 (best case) to 0 (worst case). Total scores for treatment satisfaction range from 0-36. Higher scores indicate higher satisfaction. The post-baseline responses are analysed using an ANCOVA model with treatment, country and stratification variables (HbA1c level at screening [$\leq 8.0\%$ or $> 8.0\%$] and use of metformin [yes or no]) as fixed factors and baseline value as covariate. Mean estimates are adjusted according to observed baseline distribution. Missing data was imputed using last observation carried forward. Analysis was performed on full analysis set.

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

End point timeframe:

From baseline to week 30

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|-------------------------------------|-----------------------|-----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | 2.73 (± 0.46) | 3.47 (± 0.46) | 1.25 (± 0.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c below 7.0% (53 mmol/mol) American Diabetes Association (ADA) target

| | |
|-----------------|---|
| End point title | HbA1c below 7.0% (53 mmol/mol) American Diabetes Association (ADA) target |
|-----------------|---|

End point description:

Percentage of subjects with HbA1C below 7.0% after 30 weeks treatment. Missing data imputed from a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Analysis was performed on full analysis set.

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

End point timeframe:

After 30 weeks treatment

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|-------------------------------|-----------------------|-----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 60.6 | 78.6 | 10.5 | |

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c below or equal to 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target

| | |
|-----------------|--|
| End point title | HbA1c below or equal to 6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target |
|-----------------|--|

End point description:

Percentage of subjects with HbA1C below 7.0% after 30 weeks treatment. Missing data imputed from a mixed model for repeated measurements with treatment, country and stratification variable (HbA1c level at screening [$\leq 8.0\%$ or $> 8.0\%$] crossed with use of metformin [yes or no]; 2 by 2 levels) as fixed factors and baseline value as covariate, all nested within visit. Analysis was performed on full analysis set.

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

End point timeframe:

After 30 weeks of treatment

| End point values | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo | |
|-----------------------------------|-----------------------|-----------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 132 | 131 | 133 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.9 | 61.1 | 4.5 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of trial product until the end of the post-treatment follow-up period. The follow-up visit was scheduled to take place 5 weeks after the date of last dose of trial product with a visit window of +7 days (maximum 36 weeks).

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) was defined as an AE that had onset date (or increased in severity) during the 'on-treatment' observation period.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Semaglutide 0.5 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly up to Week 30.

| | |
|-----------------------|--------------------|
| Reporting group title | Semaglutide 1.0 mg |
|-----------------------|--------------------|

Reporting group description:

Subjects received semaglutide 0.25 mg sc injection once weekly for 4 weeks followed by semaglutide 0.5 mg once weekly for next 4 weeks and then semaglutide 1.0 mg once weekly up to week 30.

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

Reporting group description:

Subjects received placebo (matched to semaglutide) sc injection once weekly for 30 weeks.

| Serious adverse events | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo |
|---|--------------------|--------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 132 (6.06%) | 12 / 131 (9.16%) | 9 / 133 (6.77%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Femoral artery occlusion | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Carotid endarterectomy | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Coronary arterial stent insertion | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (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 |
| Coronary artery bypass | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery angioplasty | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (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 |
| Peripheral artery stent insertion | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Psychiatric disorders | | | |
| Depression | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Schizophrenia | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (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 | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (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 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (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 |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| 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 | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (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 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Hypoglycaemic unconsciousness | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| 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 | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Pyelonephritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 132 (0.76%) | 0 / 131 (0.00%) | 0 / 133 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 0 / 131 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 132 (0.00%) | 1 / 131 (0.76%) | 0 / 133 (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 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Semaglutide 0.5 mg | Semaglutide 1.0 mg | Placebo |
|---|--------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 132 (39.39%) | 54 / 131 (41.22%) | 34 / 133 (25.56%) |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 12 / 132 (9.09%) | 7 / 131 (5.34%) | 4 / 133 (3.01%) |
| occurrences (all) | 15 | 7 | 4 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 132 (4.55%) | 9 / 131 (6.87%) | 2 / 133 (1.50%) |
| occurrences (all) | 6 | 9 | 2 |
| Nausea | | | |

| | | | |
|------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 15 / 132 (11.36%) | 22 / 131 (16.79%) | 6 / 133 (4.51%) |
| occurrences (all) | 21 | 23 | 6 |
| Vomiting | | | |
| subjects affected / exposed | 8 / 132 (6.06%) | 15 / 131 (11.45%) | 4 / 133 (3.01%) |
| occurrences (all) | 9 | 17 | 4 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 11 / 132 (8.33%) | 6 / 131 (4.58%) | 14 / 133 (10.53%) |
| occurrences (all) | 14 | 6 | 16 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 132 (6.06%) | 1 / 131 (0.76%) | 4 / 133 (3.01%) |
| occurrences (all) | 10 | 1 | 4 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 132 (1.52%) | 4 / 131 (3.05%) | 8 / 133 (6.02%) |
| occurrences (all) | 3 | 5 | 11 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 132 (3.79%) | 7 / 131 (5.34%) | 1 / 133 (0.75%) |
| occurrences (all) | 5 | 7 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 20 January 2015 | Change and clarify the wording of "Rescue criteria". |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported