Clinical Trial Report Synopsis

Clinical Trial Report synopsis – ICH E3 Section 2

SYNOPSIS

TRIAL TITLE

Two-year effect and safety of semaglutide 2.4 mg once weekly in subjects with overweight or obesity

Title on clinicaltrial.gov: Two-year Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity (STEP5)

TRIAL NUMBER: NN9536-4378

REGULATORY AGENCY IDENTIFIER NUMBER

clinicaltrials.gov identifier:
NCT03693430
Paediatric status:
EMEA-001441-PIP03-17-M01

UTN – U1111-1202-1740
IND number – IND 126,360
EudraCT number – 2017-003726-32

TRIAL PHASE

Phase 3b

NAME OF FINISHED PRODUCT

Semaglutide s.c. 2.4 mg

NAME OF ACTIVE SUBSTANCE

Semaglutide, NNC0113-0217

NAME OF SPONSOR/COMPANY

Novo Allé, DK-2880 Bagsvaerd, Denmark

Novo Nordisk A/S, Clinical Reporting Anchor and Disclosure (1452); email address: clinicaltrials@novonordisk.com

NUMBER OF STUDY CENTERS AND COUNTRIES

The trial was conducted at 41 sites in 5 countries as follows (all sites screened and randomised):

- Canada: 9 sites
- Hungary: 6 sites
- Italy: 5 sites
- Spain: 6 sites
- United States: 15 sites

PUBLICATIONS

No publications were available based on STEP5 data at the time of this clinical trial report synopsis.

TRIAL PERIOD

Initiation date: 05 October 2018
Primary completion date: 29 January 2021
Trial completion/termination date: 23 March 2021

DATA CUT-OFF DATE

The results presented reflect the data available in the clinical database as of 15 April 2021

BACKGROUND AND RATIONALE

This phase 3b trial was conducted as part of the development programme for semaglutide 2.4 mg in weight management, to investigate the two-year weight-reducing potential and the safety of semaglutide 2.4 mg administered once weekly as an adjunct to a reduced-calorie diet and increased physical activity, in subjects with overweight or obesity (BMI ≥27 kg/m^2) as compared to placebo. All subjects were informed of the benefits and risks of the trial and provided informed consent before any trial related activities were performed. Subjects were covered by the sponsor's insurance according to local legal requirements.

OBJECTIVES, ENDPOINTS, ESTIMANDS, AND STATISTICAL METHODS

Objectives and endpoints

The primary objective and secondary objectives of the trial are listed in Table 1 (left column) together with the endpoints defined to address these objectives (right column). In addition, exploratory objectives and endpoints not presented here were defined in the protocol.

Table -1 Objectives and endpoints

Objectives	Endpoints
Primary objective	**Primary endpoints**
To compare the two-year effect of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on body weight.	Change from baseline (week 0) to week 104 in body weight (%) Subjects who after 104 weeks achieve (yes/no): Body weight reduction ≥ 5% from baseline (week 0)
	Confirmatory and supportive secondary endpoints (confirmatory secondary endpoints are marked with an #)
	Subjects who after 104 weeks achieve (yes/no): Body weight reduction ≥ 10% from baseline (week 0)# Body weight reduction ≥ 15% from baseline (week 0)# Body weight reduction ≥ 20% from baseline (week 0) Change from baseline (week 0) to week 104 in: Waist circumference (cm)# Body weight (kg) BMI (kg/m^2)
Secondary objectives – related to efficacy	**Confirmatory and supportive secondary endpoints – efficacy endpoints** (confirmatory secondary endpoints are marked with an #)
To compare the two-year effect of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on:	***Cardiovascular risk factors*** Change from baseline (week 0) to week 104 in: Systolic blood pressure (mmHg)# Diastolic blood pressure (mmHg)

Objectives	Endpoints
Cardiovascular risk factors Glucose metabolism	Lipids (mg/dL, mmol/L) o Total cholesterol o HDL cholesterol o LDL cholesterol o VLDL cholesterol o Free fatty acids o Triglycerides CRP (mg/L) ***Glucose metabolism*** Change from baseline (week 0) to week 104 in: HbA_{1c} (%, mmol /mol) FPG (mg/dL, mmol/L) Fasting serum insulin (mIU/L, pmol/L)
To compare the one-year effect of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on body weight.	Change from baseline (week 0) to week 52 in: Body weight (%, kg) BMI (kg/m2) Waist circumference (cm) Subjects who after 52 weeks achieve (yes/no): Body weight reduction ≥ 5% from baseline (week 0) Body weight reduction ≥ 10% from baseline (week 0) Body weight reduction ≥ 15% from baseline (week 0) Body weight reduction ≥ 20% from baseline (week 0)
Secondary objectives – related to safety	**Supportive secondary endpoints** - **safety endpoints**
To compare the two-year safety and tolerability of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity.	Number of treatment emergent adverse events (TEAEs) from baseline (week 0) to week 111 Number of serious adverse events (SAEs) from baseline (week 0) to week 111 Change from baseline (week 0) to week 104 in: Pulse (bpm) Amylase (U/L) Lipase (U/L) Calcitonin (ng/L)

Estimands

The efficacy-related endpoints are evaluated for two pre-specified estimands (treatment policy and hypothetical estimand), which are used to address the trial objectives in terms of two different aspects of the treatment effect of semaglutide s.c 2.4 mg.

Primary estimand (treatment policy estimand)

This estimand will quantify the average treatment effect of semaglutide relative to placebo after 104 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity therapies (weight management drugs or bariatric surgery).

Secondary estimand (hypothetical estimand)

This estimand will quantify the average treatment effect of semaglutide relative to placebo after 104 weeks, as an adjunct to a reduced-calorie diet and increased physical activity, in all randomised subjects had they remained on their randomised treatment for the entire planned duration of the trial and not initiated other anti-obesity therapies (weight management drugs or bariatric surgery).

Statistical methods

Analysis sets

Two analysis sets were defined:

- The full analysis set (FAS) included all randomised subjects according to the intention-to-treat principle.
- The safety analysis set (SAS) included all randomised subjects exposed to at least 1 dose of randomised treatment.

Observation periods

Two observation periods were defined for each subject:

- In-trial: The in-trial period was defined as the uninterrupted time interval from date of randomisation to date of last contact with trial site.
- On-treatment (with trial product): A time-point was considered as 'on-treatment' if any dose of trial product has been administered within the prior 2 weeks (14 days). The on-treatment period is defined as all times which are considered on-treatment.

In general, the on-treatment period will therefore be from the date of first trial product administration to date of last trial product administration (±14 days) excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

For the evaluation of adverse events, the lag time for each on-treatment time interval was 7 weeks (49 days).

Sample size calculation

The sample size was primarily defined to ensure sufficient power for the two primary endpoints. The tests of superiority of semaglutide 2.4 mg to placebo for the primary and confirmatory secondary endpoints are performed using the fixed-sequence statistical strategy. This strategy tests the endpoints using a predefined hierarchical order, all at the significance level of 5%, moving to test the next endpoint only after a statistically significant superiority result (p-value < 5%) on the previous endpoint. The planned sample size of 300 subjects (150 in each arm), gave an effective power (marginal powers multiplied) of 43% for the six endpoints in the hierarchical testing procedure under the assumption that 40% of subjects discontinued permanently and 50% of these are retrieved at week 104. As sample size is primarily driven by the two primary endpoints, additional scenarios for assumptions are not included due to the high power for these endpoints.

Statistical analyses

Primary endpoints

In order to address the primary estimand, the analysis model for % weight change is a linear regression (ANCOVA) of % weight change with randomised treatment as a factor and baseline body weight (kg) as covariate, while the analysis model for the 5% responder endpoint was a logistic regression using randomised treatment as a factor and baseline body weight (kg) as covariate. Superiority tests of semaglutide 2.4 mg vs. placebo were carried out for the two analysis models. All available data at week 104 were used and missing values at week 104 were imputed and the endpoints were derived from the imputed values. A multiple imputation approach (McEvoy) was used to address the primary estimand for the primary endpoints. In addition, sensitivity analyses investigated the robustness of the estimated treatment contrasts between semaglutide 2.4 mg and placebo. For the 5% responder analysis, a sensitivity analysis using subjects with missing week 104 assessment as non-responders in the logistic regressions was also done.

The secondary estimand for % weight change was assessed using an MMRM for efficacy. The MMRM for efficacy was fitted using % weight change and the same factor and covariate as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject was employed, assuming that measurements for different subjects were independent. The secondary estimand for 5% responders was assessed using the same MMRM for efficacy except that body weight (kg) was used as response variable in the model. For subjects with missing body weight at week 104, individual values for body weight were predicted from the MMRM and used to classify each subject as 5% responder or not. This classification was then analysed using a logistic regression model with randomised treatment as a factor and baseline body weight (kg) as covariate.

Confirmatory secondary endpoints

In order to address the primary estimand, all confirmatory secondary endpoints were analysed using the same imputation approach as used for the primary endpoints with body weight replaced by assessments of the endpoint to be analysed. The statistical model for continuous endpoints was ANCOVA with factor and covariate as for the primary endpoint of % weight change with baseline body weight replaced by the baseline assessment of the endpoint to be analysed. The statistical model for body weight responder endpoints was logistic regression with factor and covariate as for the primary endpoint of 5% responders. The confirmatory secondary endpoints, which relate to the primary objective, were analysed to address the secondary estimand using the same MMRM for efficacy described for the primary endpoints.

Statistical testing strategy and hypotheses

For the evaluation of the confirmatory endpoints for the treatment policy estimand, the primary analyses were controlled for multiplicity by using a hierarchical statistical testing strategy.

Supportive secondary endpoints

In general, the supportive secondary efficacy endpoints were analysed for each estimand. The continuous as well as the responder endpoints were analysed in a similar way as the primary

endpoints of % weight change and 5% responders, respectively. The supportive secondary safety endpoint pulse was analysed using an MMRM as for efficacy. TEAEs, SAEs, amylase, lipase and calcitonin were all summarised using descriptive statistics.

METHODOLOGY

This was a 104-week, randomised, double-blind, placebo-controlled, two-armed, parallel group, multi-centre, multinational clinical trial comparing semaglutide 2.4 mg once weekly with semaglutide placebo in subjects with overweight or obesity. The trial included a screening visit to assess the subject's eligibility followed by visits/phone contacts every 2nd week during dose escalation. From week 20, visits/phone contacts took place every 4th week until end of treatment (week 104). A follow-up visit ('End of trial') for safety assessments was scheduled 7 weeks after end of treatment. Subjects with overweight or obesity were planned to receive treatment with either semaglutide 2.4 mg once weekly or placebo once weekly as an adjunct to a reduced-calorie diet and increased physical activity.

A total of 300 subjects with overweight or obesity (BMI ≥27 kg/m^2) were planned to be randomised in a 1:1 manner to receive treatment with semaglutide 2.4 mg or placebo once weekly as an adjunct to a reduced-calorie diet and increased physical activity. To mitigate the risk of GI side effects, the trial included an initial 16-week dose-escalation period during which the dose was gradually increased to the maintenance dose of 2.4 mg once weekly. Treatment continued on the maintenance dose of 2.4 mg once weekly for an additional 88 weeks until week 104 (end of treatment). Due to the long half-life of semaglutide, the follow-up visit for safety assessment was scheduled 7 weeks after end of treatment.

NUMBER OF SUBJECTS (PLANNED AND ANALYSED)

Approximately 353 subjects were planned to be screened to archive 300 subjects randomly assigned to trial product. 347 were screened and 304 were randomised and exposed. A total of 92.8% of subjects completed the trial (Table 2).

Table -2 Subject disposition - summary - all subjects

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Screened			347
Screening failures			42
Withdrawn before randomisation			1
Randomised	152 (100)	152 (100)	304 (100)
Randomised in violation of incl., excl. and/or randomisation criteria	2 (1.3)	1 (0.7)	3 (1.0)
Exposed	152 (100)	152 (100)	304 (100)
Analysis sets			
Full analysis set	152 (100)	152 (100)	304 (100)
Safety analysis set	152 (100)	152 (100)	304 (100)
Treatment completion			
On-treatment at week 104 (treatment completers)	132 (86.8)	111 (73.0)	243 (79.9)
After at least one temporary interruption	19 (12.5)	10 (6.6)	29 (9.5)
Attended end-of-treatment visit without permanent discontinuation of trial product	132 (86.8)	111 (73.0)	243 (79.9)
Trial product permanently discontinued	20 (13.2)	41 (27.0)	61 (20.1)
Primary reason for permanent discontinuation of trial product			
Adverse event	10 (6.6)	7 (4.6)	17 (5.6)
Protocol violation	0	1 (0.7)	1 (0.3)
Simultaneous participation in another clinical trial	0	1 (0.7)	1 (0.3)
Pregnancy	1 (0.7)	0	1 (0.3)
Lack of efficacy	2 (1.3)	7 (4.6)	9 (3.0)
Safety concern as judged by the investigator	1 (0.7)	1 (0.7)	2 (0.7)
Withdrawal of consent	0	4 (2.6)	4 (1.3)
Lost to follow-up	3 (2.0)	12 (7.9)	15 (4.9)
Other	3 (2.0)	9 (5.9)	12 (3.9)
Attended end-of-treatment visit after permanent discontinuation of trial product	16 (10.5)	26 (17.1)	42 (13.8)
Trial completion			
Attended end-of-trial visit (trial completers)	148 (97.4)	134 (88.2)	282 (92.8)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	132 (86.8)	110 (72.4)	242 (79.6)
Withdrawn from trial	4 (2.6)	18 (11.8)	22 (7.2)
Primary reason for trial withdrawal			
Withdrawal by subject	0	4 (2.6)	4 (1.3)
Lost to follow-up	3 (2.0)	14 (9.2)	17 (5.6)
Death	1 (0.7)	0	1 (0.3)
Withdrawn from trial before week 104	4 (2.6)	16 (10.5)	20 (6.6)
Withdrawn from trial without prior permanent discontinuation of trial product	1 (0.7)	4 (2.6)	5 (1.6)

N: Number of subjects, %: Percentages are based on randomised subjects.
A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 104). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 104).
Only reasons for permanent discontinuation of trial product or trial withdrawal actually recorded for at least one subject are presented.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION

Key inclusion criteria

- Male or female, age ≥18 years at the time of signing informed consent
- Body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease
- History of at least one self-reported unsuccessful dietary effort to lose body weight

Key exclusion criteria

- HbA_{1c} ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening
- A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records

Randomisation criteria

- Have kept a food diary with at least one entry per day between screening and randomisation. However, missed entries for a maximum of two days were allowed
- A PHQ-9 score of <15 at randomisation
- No suicidal behaviour in the period between screening and randomisation
- No suicidal ideation corresponding to type 4 or 5 on the C-SSRS in the period between screening and randomisation
- Discontinuation criteria
- Safety concern as judged by the investigator
- Calcitonin ≥100 ng/L
- Suspicion of pancreatitis
- Pregnancy
- Intention of becoming pregnant
- Simultaneous participation in another clinical trial of an approved or non-approved investigational medicinal product

TRIAL INTERVENTION, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER(S)

Semaglutide (product code: NNC0113-0217) was administered using a PDS290 pre-filled pen-injector with a 3 mL cartridge containing semaglutide 1.0 mg/mL or 3.0 mg/mL (depending on dose level). Dose escalation was to take place during the first 16 weeks after randomisation with dose increase every 4 weeks (from 0.25 mg/week to doses of 0.5, 1.0, 1.7 and 2.4 mg/week). If a subject could not tolerate the recommended dose of semaglutide 2.4 mg, the subject could stay at a lower dose level. The reference therapy was semaglutide placebo; dose escalation was performed as for semaglutide.

The batch numbers and expiry dates for semaglutide are as follows:

- 1.0 mg/mL (for doses of 0.25 mg and 0.5 mg once weekly): HP50620 (18-April-2020)

- 3.0 mg/mL (for doses of 1.0 mg, 1.7 mg and 2.4 mg once weekly): HP50623 (13-September-2020), HP53043 (05-October-2020), JP51975 (06-June-2021), JP53369 (06-June-2021)
- The batch numbers and expiry dates for semaglutide placebo are as follows:
- HP51152 (13-September-2020), HP53677 (06-June-2021)

DURATION OF TRIAL INTERVENTION

104 weeks

SUMMARY OF RESULTS AND CONCLUSIONS

Demographics and other baseline characteristics

Demographics and other baseline clinical characteristics were overall well-balanced across the two treatment groups (Table 3).

Table -3 Demographics and baseline characteristics - summary

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	152	152	304
Age (years)			
N	152 (100)	152 (100)	304 (100)
18-<65	140 (92.1)	145 (95.4)	285 (93.8)
65-<75	11 (7.2)	7 (4.6)	18 (5.9)
75-<85	1 (0.7)	0	1 (0.3)
>=85	0	0	0
Sex			
N	152 (100)	152 (100)	304 (100)
Female	123 (80.9)	113 (74.3)	236 (77.6)
Male	29 (19.1)	39 (25.7)	68 (22.4)
BMI (kg/m^2)			
N	152 (100)	152 (100)	304 (100)
<30	6 (3.9)	3 (2.0)	9 (3.0)
30-<35	47 (30.9)	58 (38.2)	105 (34.5)
35-<40	49 (32.2)	33 (21.7)	82 (27.0)
>=40	50 (32.9)	58 (38.2)	108 (35.5)
Body weight (kg)			
N	152	152	304
Mean (SD)	105.6 (20.8)	106.5 (23.1)	106.0 (22.0)
Median	100.8	102.8	102.1
P5 ; P95	78.4 ; 141.9	77.0 ; 143.8	78.4 ; 143.5
Min ; Max	68.3 ; 197.5	65.4 ; 251.4	65.4 ; 251.4
BMI (kg/m^2)			
N	152	152	304
Mean (SD)	38.6 (6.7)	38.5 (7.2)	38.5 (6.9)
Median	38.0	36.7	37.6
P5 ; P95	30.2 ; 50.5	30.5 ; 50.1	30.4 ; 50.3
Min ; Max	27.6 ; 63.5	27.7 ; 82.7	27.6 ; 82.7
Waist circumference (cm)			
N	152	152	304
Mean (SD)	115.8 (14.3)	115.7 (15.5)	115.7 (14.8)
Median	114.0	113.0	114.0
P5 ; P95	95.0 ; 142.0	95.1 ; 142.2	95.1 ; 142.0
Min ; Max	83.0 ; 166.0	88.0 ; 193.4	83.0 ; 193.4
HbA1c (%)			
N	152	152	304
Mean (SD)	5.7 (0.3)	5.7 (0.4)	5.7 (0.3)
Median	5.7	5.7	5.7
P5 ; P95	5.2 ; 6.3	5.2 ; 6.3	5.2 ; 6.3
Min ; Max	4.9 ; 6.5	4.8 ; 7.0	4.8 ; 7.0

N: Number of subjects, %: Percentages are based on number of subjects, BMI: Body mass index.
The last available and eligible observation at or prior to the randomisation visit was selected for summary.

Efficacy results

In this trial, the treatment effect of semaglutide 2.4 mg administered once weekly as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity, was evaluated vs placebo.

From baseline to week 104, superiority of semaglutide 2.4 mg vs placebo was confirmed in the pre-defined fixed-sequence statistical testing hierarchy for the primary endpoints (change in body weight [%] and body weight loss ≥5%) and all confirmatory secondary endpoints (body weight loss

≥10%, body weight loss ≥15%, change in waist circumference and systolic blood pressure). Results are presented below together with related endpoints.

Body weight

Superiority of semaglutide 2.4 mg vs placebo was confirmed for the two primary endpoints:

- Body weight change (%) from baseline to week 104: −15.18% vs −2.62%; ETD: −12.55% [−15.33; −9.77]$_{95\%CI}$
- Proportion of subjects achieving a body weight reduction ≥5% at week 104: 77.1% vs 34.4%; odds ratio: 4.99 [2.95; 8.42]$_{95\%CI}$
- The pre-specified sensitivity analyses supported this conclusion

Results for the weight-related secondary efficacy endpoints from baseline to week 104 were also in favour of semaglutide 2.4 mg vs placebo:

- Superiority of semaglutide 2.4 mg vs placebo was confirmed for the proportion of subjects achieving the pre-defined categorical weight reductions of:
- ≥10%: 61.6% vs 13.3%; odds ratio: 7.23 [3.95;13.23]$_{95\%\ CI}$
- ≥15%: 52.1% vs 7.0%; odds ratio: 9.40 [4.41; 20.04]$_{95\%\ CI}$
- A greater proportion of subjects achieved the pre-defined categorical weight reduction with semaglutide 2.4 mg vs placebo of:
- ≥20%: 36.1% vs 2.3%; odds ratio: 12.84 [3.94; 41.88]$_{95\%\ CI}$
- The decrease in mean waist circumference was superior for semaglutide 2.4 mg vs placebo:
- −14.36 cm vs −5.19 cm; ETD: −9.17 cm [−12.17; −6.17]$_{95\%CI}$
- The decrease in mean body weight (kg) was greater with semaglutide 2.4 mg vs placebo.
- The decrease in mean BMI was greater with semaglutide 2.4 mg vs placebo.
- Weight-related endpoints were also assessed at week 52:
- Change in mean body weight (%) was −15.59% with semaglutide 2.4 mg and −2.99% with placebo; ETD: −12.59% [−14.45; −10.74]$_{95\%\ CI}$
- Body weight reduction ≥5%: 88.6 % vs 29.5%; (semaglutide 2.4 mg vs placebo): odds ratio: 18.64 [9.81; 35.42]$_{95\%\ CI}$
- A greater proportion of subjects achieved the weight reduction of ≥10%, ≥15% and ≥20% with semaglutide 2.4 mg vs placebo
- The decreases in mean waist circumference, mean body weight (kg) and mean BMI were greater with semaglutide 2.4 mg vs placebo.

Cardiovascular risk factors

- The decrease in mean systolic blood pressure from baseline to week 104 was superior for semaglutide 2.4 mg vs placebo:
- −5.74 mmHg vs −1.59 mmHg; ETD: −4.15 mmHg [−7.32; −0.98]$_{95\%\ CI}$
- The decrease in mean diastolic blood pressure from baseline to week 104 was greater for semaglutide 2.4 mg vs placebo:
- −4.45 mmHg vs −0.78 mmHg; ETD: −3.66 mmHg [−6.13; −1.20]$_{95\%\ CI}$

- From baseline to week 104, beneficial effects in favour of semaglutide 2.4 mg vs placebo were seen for total cholesterol, VLDL cholesterol and triglycerides, and for CRP.

Glucose metabolism

- From baseline to week 104, glucose metabolism (as assessed by HbA_{1c}, FPG and fasting serum insulin) improved with semaglutide 2.4 mg vs placebo

Control of eating questionnaire (CoEQ)

- From baseline to week 104, the two domains Craving Control and Craving for Savoury improved with semaglutide 2.4 mg vs placebo.

Safety results

The proportion of subjects with AEs, and the rate of AEs reported, were higher with semaglutide 2.4 mg than with placebo (96.1%, 532.3 events per 100 PYE versus 89.5%, 374.8 events per 100 PYE), driven primarily by gastrointestinal AEs. The relative distribution of AEs with respect to seriousness, severity and outcome were comparable across both arms, with most being non-serious, of mild or moderate severity, and reported as recovered.

Summary of adverse events

A greater proportion of events were considered probably or possibly related to trial product in the semaglutide arm than with placebo (80.9%, 243.3 per 100 PYE versus 50.7%, 99.7 per 100 PYE). GI symptoms are a well-known side-effect of GLP-1 RA treatment, thus the higher rate of attributing causality to trial product in the semaglutide arm likely reflects the greater proportion of GI events reported in this arm.

Similarly, a higher proportion of subjects in the semaglutide arm compared to placebo reduced their dose (11.2% versus 0.7%), temporarily interrupted treatment (14.5% versus 8.6%), or permanently discontinued treatment (5.9% versus 4.6%), due to AEs.

The proportion of subjects with SAEs was lower with semaglutide 2.4 mg than with placebo (7.9% vs 11.8%), however the rates of reporting SAEs were similar (6.0 vs 7.5 events per 100 PYE). In both treatment arms, most SAEs occurred in the SOC Infections and infestations. The SAEs in both arms were distributed, in low numbers, across several preferred terms, with no evident patterning. In the semaglutide arm, there was a small concentration (4 events in 3 subjects) of SAEs in the SOC Hepatobiliary disorders (PTs cholelithiasis, cholecystitis), and in the placebo arm a small group (4 events in 4 subjects) in the SOC Neoplasms, benign, malignant and unspecified.

One death, due to acute myocardial infarction, occurred during the trial. The investigator added an alternative aetiology of underlying disease (coronary atherosclerosis).

For most of the predefined safety focus areas, no treatment differences were evident between the semaglutide and placebo arms. For GI, acute gallbladder, allergic reactions, and hypoglycaemic events, the proportion and rate of events was higher in the semaglutide arm compared to placebo. For cardiovascular events and medication errors, the proportion and rate of events was lower for semaglutide compared to placebo. No events related to acute pancreatitis, acute renal failure, or suspected transmission of an infectious agent via trial product, were reported.

Clinical laboratory evaluations

No clinically relevant treatment differences were noted in the laboratory biochemistry parameters.

Four events (in 3 subjects) of elevated biochemistry levels (ALT, AST) that exceeded the safety thresholds occurred: 2 in the semaglutide arm, and 2 in placebo. None of the events fulfilled the definition of Hy's law.

Geometric mean levels of amylase and lipase remained within the normal reference range throughout the on-treatment period in both treatment arms. In the semaglutide arm, estimated ratios to baseline indicate a slight increase in amylase (13%), and a greater increase in lipase (47%), during the treatment period. The increases in both amylase and lipase in the semaglutide arm were lower in the second year of the trial. In the placebo arm, mean levels of amylase and lipase remained near baseline throughout the trial.

Estimated mean calcitonin levels in both treatment arms remained close to baseline levels throughout the course of the on-treatment period. No events of individual elevations of calcitonin met the diagnostic criteria of >100 ng/L during the on-treatment period.

Overall, the proportion of subjects with increased pulse were greater in the semaglutide arm than for placebo. The estimated treatment difference between the semaglutide and placebo arms at week 104 was statistically significant (4.14 beats/min (CI 2.05; 6.24, p-value 0.0001)). After 7 weeks off-treatment, the median pulse rates of the semaglutide (74 beats/min) and placebo (76 beats/min) arms were comparable.

Pulse

Overall, the proportion of subjects with increased pulse were greater in the semaglutide arm than for placebo. The estimated treatment difference between the semaglutide and placebo arms at week 104 was statistically significant (4.14 beats/min (CI 2.05; 6.24)). After 7 weeks off-treatment, the median pulse rates of the semaglutide (74 beats/min) and placebo (76 beats/min) arms were comparable.

CONCLUSIONS

For the present trial conducted in subjects with overweight or obesity randomised to 104 weeks of treatment with semaglutide 2.4 mg or placebo as an adjunct to a reduced-calorie diet and increased physical activity, the following is concluded:

- Semaglutide 2.4 mg was superior to placebo with respect to weight loss (−15.18% vs −2.62%; ETD: −12.55% [−15.33; −9.77]$_{95\% CI}$), including 5%, 10 % and 15% weight loss responders, waist circumference and systolic blood pressure
- Improvements for semaglutide 2.4 mg vs placebo were also observed for cardiovascular risk-related factors and glucose metabolism
- Semaglutide 2.4 mg was overall well tolerated and the safety and tolerability profile were consistent with the GLP-1 RA class in general

DATE AND VERSION OF THIS REPORT

17 August 2021

COMPLIANCE STATEMENT

The trial was conducted in accordance with the Declaration of Helsinki (2013), ICH Good Clinical Practice (2016) and FDA 21 CFR 312.120.