Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial

Christopher Sorli, Shin-ichi Harashima, George M Tsoukas, Jeffrey Unger, Julie Derving Karsbøl, Thomas Hansen, Stephen C Bain

Summary

Background Despite a broad range of pharmacological options for the treatment of type 2 diabetes, optimum glycaemic control remains challenging for many patients and new therapies are necessary. Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue in phase 3 development for type 2 diabetes. We assessed the efficacy, safety, and tolerability of semaglutide monotherapy, compared with placebo, in treatment-naive patients with type 2 diabetes who had insufficient glycaemic control with diet and exercise alone.

Methods We did a double-blind, randomised, parallel-group, international, placebo-controlled phase 3a trial (SUSTAIN 1) at 72 sites in Canada, Italy, Japan, Mexico, Russia, South Africa, UK, and USA (including hospitals, clinical research units, and private offices). Eligible participants were treatment-naive individuals aged 18 years or older with type 2 diabetes treated with only diet and exercise alone for at least 30 days before screening, with a baseline HbA$_{1c}$ of 7·0%–10·0% (53–86 mmol/mol). We randomly assigned participants (2:2:1:1) to either once-weekly subcutaneously injected semaglutide (0·5 mg or 1·0 mg), or volume-matched placebo (0·5 mg or 1·0 mg), for 30 weeks via prefilled PDS290 pen-injectors. Participants did their own injections and were encouraged to administer them on the same day of each week in the same area of their body; the time of day and proximity of meal times was not specified. We did the randomisation with an interactive voice or web response system. Investigators, participants, and the funder of the study remained masked throughout the trial. The primary endpoint was the change in mean HbA$_{1c}$ from baseline to week 30, and the confirmatory secondary endpoint was the change in mean bodyweight from baseline to week 30. We assessed efficacy and safety in the modified intention-to-treat population (ie, all participants who were exposed to at least one dose of study drug); both placebo groups were pooled for assessment. This trial was registered with ClinicalTrials.gov, number NCT02054897.

Findings Between February 3, 2014, and August 21, 2014, we randomly assigned 388 participants to treatment; 387 received at least one dose of study medication (128 0·5 mg semaglutide, 130 1·0 mg semaglutide, 129 placebo). 17 (13%) of those assigned to 0·5 mg semaglutide, 16 (12%) assigned to 1·0 mg semaglutide, and 14 (11%) assigned to placebo discontinued treatment; the main reason for discontinuation was gastrointestinal adverse events such as nausea. Mean baseline HbA$_{1c}$ was 8·05% (SD 0·85); at week 30, HbA$_{1c}$ significantly decreased by 1·45% (95% CI –1·65 to –1·26) with 0·5 mg semaglutide (estimated treatment difference *vs* placebo –1·43%, 95% CI –1·71 to –1·15; p<0·0001), significantly decreased by 1·55% (–1·74 to –1·36) with 1·0 mg semaglutide (estimated treatment difference *vs* placebo –1·53%, –1·81 to –1·25; p<0·0001), and non-significantly decreased by 0·02% (–0·23 to 0·18) with placebo. Mean baseline bodyweight was 91·93 kg (SD 23·83); at week 30, bodyweight significantly decreased by 3·73 kg (95% CI –4·54 to –2·91) with 0·5 mg semaglutide (estimated treatment difference *vs* placebo –2·75 kg, 95% CI –3·92 to –1·58; p<0·0001), significantly decreased by 4·53 kg (–5·34 to –3·72) with 1·0 mg semaglutide (estimated treatment difference *vs* placebo –3·56 kg, –4·74 to –2·38; p<0·0001), and non-significantly decreased by 0·98 kg (–1·82 to –0·13) with placebo. No deaths were reported in any of the study groups and most reported adverse events were of mild or moderate severity. The most frequently reported adverse events in both semaglutide groups were gastrointestinal in nature: nausea was reported in 26 (20%) who received 0·5 mg semaglutide, 31 (24%) who received 1·0 mg semaglutide, and 10 (8%) who received placebo, and diarrhoea was reported in 16 (13%) who received 0·5 mg semaglutide, 14 (11%) who received 1·0 mg semaglutide, and three (2%) who received placebo.

Interpretation Semaglutide significantly improved HbA$_{1c}$ and bodyweight in patients with type 2 diabetes compared with placebo, and showed a similar safety profile to currently available GLP-1 receptor agonists, representing a potential treatment option for such patients.

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**Billings Clinic Research Center,
Billings, MT, USA** (C Sorli MD);
**Graduate School of Medicine,
Kyoto University, Kyoto, Japan**
(S-i Harashima MD);
**Department of Medicine,
McGill University, Montreal,
QC, Canada** (G M Tsoukas MD);
**Catalina Research Institute,
Chino, CA, USA** (J Unger MD);
**Novo Nordisk A/S, Søborg,
Denmark** (J D Karsbøl MD,
T Hansen PhD); **School of
Medicine, Swansea University,
Swansea, Wales, UK**
(Prof S C Bain FRCP)

Correspondence to:
Dr Christopher Sorli, Billings
Clinic, 1045 North 30th Street,
Billings, MT 59101, USA
chrissorli@gmail.com

Research in context

Evidence before this study
We designed this study on the basis of evidence obtained from the clinical development of semaglutide, including in-vitro receptor studies, carcinogenicity studies, studies of prenatal and postnatal developmental toxicity, phase 1 single-dose and multi-dose pharmacokinetic studies and pharmacodynamic studies, and a phase 2 dose-finding trial. Several long-acting glucagon-like peptide-1 (GLP-1) receptor agonists with pharmacokinetic properties suitable for once-weekly dosing have been approved for the treatment of type 2 diabetes. The currently available products include albiglutide, exenatide extended release, and dulaglutide. Biochemical methods of protraction differ and whether the molecular properties of long-acting GLP-1 receptor agonists will have differential influences on efficacy or safety parameters is unknown. We note that there was a risk of bias in the published scientific literature; ie, that positive results might have been preferentially reported for compounds with therapeutic implications.

Added value of this study
The findings from this study showed that use of semaglutide, a once-weekly GLP-1 analogue, achieved a high degree of glycaemic control with weight loss in patients with type 2 diabetes, without an increased risk of hypoglycaemia. The safety profile of semaglutide seems to be similar to available GLP-1 receptor agonists, consisting mainly of gastrointestinal events such as nausea and diarrhoea.

Implications of all the available evidence
Compared with other available once-weekly GLP-1 receptor agonists, semaglutide has a low molecular weight and a distinctive method of protraction based on its affinity to albumin. Results from this study indicate that semaglutide significantly improves glycaemic control in patients with type 2 diabetes. Indirect comparison of data from this study with data from similar GLP-1 receptor agonist monotherapy trials indicates that improvements in glycaemic control with semaglutide are similar and the extent of weight loss is greater with semaglutide than has been reported for other GLP-1 receptor agonists. However, head-to-head trials are needed to draw firm conclusions on the relative efficacy of semaglutide and other GLP-1 receptor agonists.

Introduction

Type 2 diabetes is a complex disorder that requires individualised treatment strategies. In addition to diet and lifestyle changes, pharmacotherapy is usually required.[1] A range of therapies are now available for treatment of type 2 diabetes, including orally administered and injectable options.[1] However, despite this broad range of therapeutic options, optimum glycaemic control remains challenging for many patients and new therapies are necessary. Guidelines recommend avoidance of both hypoglycaemia and weight gain as important therapeutic considerations when selecting treatments and individualising treatment goals.[1,2]

Glucagon-like peptide-1 (GLP-1) receptor agonists stimulate insulin secretion and inhibit the release of glucagon in a glucose-dependent manner, which results in improved blood glucose concentrations combined with a low risk of hypoglycaemia.[3] Unlike many other therapies for type 2 diabetes, GLP-1 receptor agonists have been shown to reduce bodyweight[4] as a consequence of reduced appetite and energy intake,[5] as well as modifying patients' perception of food.[6]

Short-acting GLP-1 receptor agonists that require administration once or twice per day were the first drugs in this class to be developed. Recent efforts have focused on developing GLP-1 receptor agonists that require less frequent dosing, with a view to reducing treatment burden and improving patient adherence.[7] Currently, three GLP-1 receptor agonists are available that can be administered once-weekly: exenatide extended release, albiglutide, and dulaglutide.[8]

Semaglutide is a GLP-1 analogue in development for the treatment of type 2 diabetes. It has 94% structural homology to natural GLP-1, and is based on the same technology as liraglutide, another GLP-1 receptor agonist.[9] Semaglutide is more resistant than liraglutide to degradation via dipeptidyl peptidase-4 (DPP-4) and has increased affinity to albumin. As a result, semaglutide has a half-life of approximately 1 week, rendering it appropriate for once-weekly subcutaneous administration.[9] Semaglutide has a low molecular weight, so is likely to reach the brain in a manner similar to that described for liraglutide.[10]

This Article reports the findings of our phase 3a trial, SUSTAIN 1, which assessed once-weekly subcutaneous semaglutide given at doses of 0·5 mg and 1·0 mg. We assessed the efficacy, safety, and tolerability of semaglutide monotherapy compared with placebo, in treatment-naive patients with type 2 diabetes who had insufficient glycaemic control with diet and exercise alone.

Methods

Study design and participants

We did a phase 3a, randomised, double-blind, parallel-group, multinational, multicentre trial (SUSTAIN 1) at 72 sites in Canada (seven), Italy (six), Japan (five), Mexico (two), Russia (eight), South Africa (eight), UK (four), and USA (32). Sites included hospitals, clinical research units, and private offices. The study protocol was approved by either institutional review boards or ethics committees at each site, according to local practice.

Eligible participants were adults aged 18 years or older with type 2 diabetes treated with diet and exercise alone for at least 30 days before screening when enrolled and an HbA$_{1c}$ of 7·0%–10·0% (53–86 mmol/mol). We recruited some participants using advertisements at some sites. Key exclusion criteria included treatment with glucose-lowering drugs in the 90 days before screening (except for short-term [≤7 days] treatment with insulin), history of chronic or idiopathic acute pancreatitis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min per 1·73 m²), screening calcitonin values of at least 50 ng/L (pg/mL), heart failure (New York Heart Association class IV), or any acute coronary or cerebrovascular events in the 90 days before randomisation. Full eligibility criteria are in the appendix. We obtained written informed consent from all participants before commencement of any study-related activities.

Randomisation and masking

We randomly assigned participants (2:2:1:1) with no restrictions, using an interactive voice or web response system, to receive either once-weekly subcutaneously injected semaglutide (0·5 mg or 1·0 mg) or once-weekly volume-matched placebo (0·5 mg or 1·0 mg), ensuring masking within dose. The random assignment to trial groups was done by an automated voice/web recognition system without human involvement. Placebo and active drug were provided in prefilled 1·5 mL PDS290 pen-injectors and were identical in appearance, taste, and smell. Equal volumes of placebo and active drug were administered within each dose. The investigators, participants, and study funder remained masked throughout the trial.

Procedures

After a 2-week screening period, participants received subcutaneously injected semaglutide 0·5 mg or 1·0 mg or volume-matched placebo once per week for 30 weeks, followed by a 5-week follow-up period (appendix). Participants administered their own injections and were encouraged to administer them on the same day of each week in the same area of their body (thigh, abdomen, or upper arm); the time of day and proximity of meal times was not specified. Participants were encouraged to inject in the same area throughout the trial because data for semaglutide blood concentrations were collected for future population pharmacokinetic analyses to assess equivalence between injection sites.

The trial implemented complete follow-up for all participants, including those who discontinued treatment prematurely. All participants in the semaglutide groups followed a fixed-dose escalation regimen, with a corresponding volume-matched escalation in the placebo groups. In the semaglutide 0·5 mg group, the maintenance dose was reached after 4 weeks of 0·25 mg semaglutide once per week. In the semaglutide 1·0 mg group, the maintenance dose was reached after 4 weeks of 0·25 mg semaglutide, followed by 4 weeks of 0·5 mg semaglutide. Participants with unacceptable hyperglycaemia (ie, any fasting plasma glucose [FPG] value more than 270 mg/dL [15·0 mmol/L] from baseline to week 6, 240 mg/dL [13·3 mmol/L] from week 6 to week 12, or 200 mg/dL [11·1 mmol/L] from week 12 to end of trial; appendix) could be offered metformin (first choice) or other antidiabetic medications (but not GLP-1 receptor agonists or DPP-4 inhibitors) as add-ons to their study treatment as rescue medication at the discretion of the investigator, in accordance with treatment guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[1]

Outcomes

The primary endpoint was the change in mean HbA$_{1c}$ concentrations from baseline to week 30 with semaglutide versus placebo, assessed at a central laboratory. The confirmatory secondary endpoint was the change in mean bodyweight from baseline to week 30. Other secondary efficacy endpoints measured at 30 weeks were the proportion of participants who achieved HbA$_{1c}$ less than 7·0% (53 mmol/mol) or HbA$_{1c}$ of 6·5% or less (48 mmol/mol) by the end of treatment; a composite endpoint of HbA$_{1c}$ less than 7·0% with no severe hypoglycaemia (according to the ADA classification[11]) or blood glucose-confirmed hypoglycaemia (<3·1 mmol/L [56 mg/dL] with symptoms consistent with hypo-glycaemia) and no weight gain; change from baseline to week 30 in fasting plasma glucose (FPG); self-measured plasma glucose (SMPG) seven-point profiles and prandial increments (over all meals); laboratory measurements associated with β-cell function and glycaemic control (insulin, C-peptide, pro-insulin, glucagon, proinsulin to insulin ratio, and a homeostasis model assessment of β-cell function [HOMA-B] and insulin resistance [HOMA-IR], all fasting); proportion of participants who achieved weight loss of at least 5%, and of those who achieved at least 10%, from baseline to week 30; BMI; waist circumference; fasting blood lipids; and systolic and diastolic blood pressure.

Safety endpoints were the number of treatment-emergent adverse events and the number of severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during exposure, and pulse rate. Other safety measurements were changes in laboratory variables (haematology, biochemistry, calcitonin, urinalysis, and urinary albumin-to-creatinine ratio) and examinations (electrocardiogram and physical examination) at week 30, the occurrence and concentration of antisemaglutide antibodies, and semaglutide pharma-cokinetics (to be included in future population pharmacokinetic analyses across semaglutide phase 3a trials). According to US Food and Drug Administration requirements, and in an independent and masked manner, an external adverse event adjudication committee (EAC) validated predefined events (appendix).

See **Online** for appendix

Statistical analysis

The two placebo groups were pooled for efficacy and safety assessments. We designed the trial with 80% power to detect significant differences for both doses of semaglutide versus pooled placebo (hereafter referred to as placebo) for both HbA$_{1c}$ and bodyweight at week 30 with a one-sided α-value of 2·5%, assuming treatment differences versus placebo of 0·45% and 2·25 kg, respectively, for each semaglutide dose, and SDs of 1·1% and 4·0 kg, respectively. The type-I error probability was controlled at 2·5% (one-sided) across the four hypotheses; superiority was assessed with a hierarchical testing strategy detailed here and in the appendix. On the basis of these assumptions, we calculated that the sample size would need to be 390, accounting for 20% missing data in the semaglutide group and 30% in the placebo group. We first tested the HbA$_{1c}$ endpoint for semaglutide versus placebo, starting with semaglutide 1·0 mg followed by 0·5 mg, then the bodyweight endpoint for semaglutide versus placebo in the same dose order (appendix).

We assessed efficacy in a modified intention-to-treat (ITT) analysis, comprising all randomly assigned participants who were exposed to at least one dose of study drug or placebo; the assessment used data obtained before initiation of any rescue medication or before premature treatment discontinuation. Safety was assessed in the same study population. For the safety assessment, we used only data obtained before premature treatment discontinuation with an ascertainment window of 42 days to identify treatment-emergent adverse events. We did supportive analyses using all data obtained during the trial for both efficacy and safety.

Analysis methods for HbA$_{1c}$, bodyweight, and other continuous endpoints assessed over time included a mixed model for repeated measurements (MMRM), with factors for treatment, country, and baseline values, all nested within visits. All p values were two-sided for the null hypothesis of no treatment difference. We assessed the robustness of the analyses of HbA$_{1c}$ and bodyweight by handling missing data in various ways in analyses, including a placebo-based multiple imputation model for which missing data points were imputed as if the participant had been treated with placebo. We did sensitivity analyses that also included an MMRM analysis on the modified ITT population using all data, regardless of whether data had been obtained while the participants had discontinued study drugs or whether the participant had been given rescue medication (appendix). A data safety monitoring committee was not involved in this study. We used SAS version 9.4 for all analyses. This trial was registered with ClinicalTrials.gov, number NCT02054897.
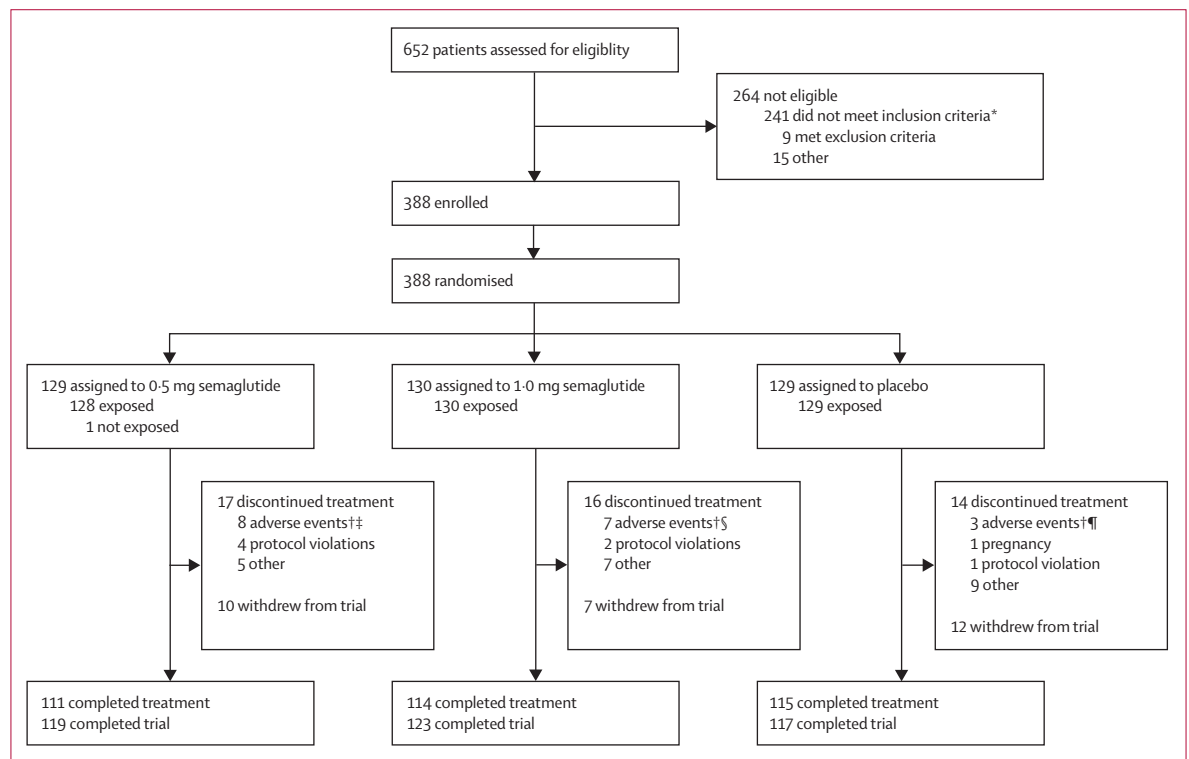

***Figure 1:* Trial profile**
*Participants did not have an HbA$_{1c}$ within the specified range. †Main reason for treatment discontinuation, as judged by the investigator. ‡3 participants discontinued because of gastrointestinal adverse events and 5 because of other adverse events. §3 participants discontinued because of gastrointestinal adverse events and 4 because of other adverse events. ¶No participants discontinued because of gastrointestinal adverse events and 3 because of other adverse events.

Role of the funding source

The funder participated in discussions regarding study design and protocol development, and provided logistical support during the trial. The funder obtained the data, which were assessed jointly by the authors and the sponsor. The authors interpreted the data, and wrote the report with medical writing services provided by the funder. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 3, 2014, and Aug 21, 2014, we randomly assigned 388 participants to treatment; 387 received at least once dose of trial medication (128 received 0·5 mg semaglutide, 130 received 1·0 mg semaglutide, and 129 received placebo; figure 1). The number of participants administered rescue medication was six (5%) each with 0·5 mg and 1·0 mg semaglutide, compared with 24 (21%) with placebo (no comparative statistics were done here because this was not an outcome). The number of participants discontinuing treatment prematurely was 17 (13%) with 0·5 mg semaglutide, 16 (12%) with 1·0 mg semaglutide, and 14 (11%) with placebo. The main reason for premature treatment discontinuation was adverse events (figure 1).

Baseline characteristics were similar between the three groups (table 1) in regard to mean diabetes duration, HbA_{1c}, BMI, and eGFR. Mean bodyweight was numerically higher in the 1·0 mg semaglutide group than in the 0·5 mg semaglutide and placebo groups. There were also numerically more male participants in the 1·0 mg semaglutide group, compared with the 0·5 mg semaglutide and placebo groups.

Mean HbA_{1c} (baseline 8·05%, SD 0·85) decreased at a similar rate over time in both semaglutide groups (figure 2, appendix). At week 30, HbA_{1c} had significantly decreased by 1·45% (95% CI −1·65 to −1·26) with 0·5 mg semaglutide (estimated treatment difference *vs* placebo −1·43%, 95% CI −1·71 to −1·15; p<0·0001), and significantly decreased by 1·55% (−1·74 to −1·36) with 1·0 mg semaglutide (estimated treatment difference *vs* placebo −1·53%, −1·81 to −1·25; p<0·0001), versus a non-significant decrease of 0·02% (−0·23 to 0·18) with placebo (figure 2, table 2). HbA_{1c} less than 7·0% was achieved by significantly more participants in the semaglutide groups versus the placebo group (p<0·0001 for both; table 3). This target was achieved without severe or blood-glucose-confirmed hypoglycaemia and without weight gain in significantly more participants in the 0·5 mg and 1·0 mg semaglutide groups compared with the placebo group (table 3). Likewise, HbA_{1c} of 6·5% or less was achieved by significantly more participants in the 0·5 mg and 1·0 mg semaglutide groups than in the placebo group (p<0·0001 for both; table 3).

At week 30, mean FPG and mean seven-point SMPG were significantly reduced with 0·5 mg and 1·0 mg semaglutide (p<0·0001 for both variables in both groups versus placebo; table 2). The reduction in mean seven-point SMPG post-meal increment was significantly greater with 1·0 mg semaglutide versus placebo but not with 0·5 mg semaglutide versus placebo (table 2).

Proinsulin and the proinsulin to insulin ratio were significantly reduced, and C-peptide and HOMA-B were significantly increased, with both doses of semaglutide versus placebo. HOMA-IR was significantly reduced with 1·0 mg semaglutide compared with placebo; this variable was numerically decreased with 0·5 mg semaglutide compared with placebo but this decrease was not significant. No significant changes in fasting insulin or plasma glucagon levels were noted (appendix).

Mean baseline bodyweight was 91·93 kg (SD 23·83). At week 30, bodyweight significantly decreased by 3·73 kg (95% CI −4·54 to −2·91) with 0·5 mg semaglutide (estimated treatment difference *vs* placebo −2·75 kg, 95% CI −3·92 to −1·58; p<0·0001), and significantly decreased by 4·53 kg (−5·34 to −3·72) with 1·0 mg semaglutide (estimated treatment difference *vs* placebo −3·56 kg, −4·74 to −2·38; p<0·0001), versus a decrease of 0·98 kg with placebo (−1·82 to −0·13; figure 2, table 2). A similar pattern of weight change over time occurred in both semaglutide groups (appendix). Bodyweight reductions of at least 5% and 10% were achieved by significantly more participants in the 0·5 mg and 1·0 mg semaglutide groups than in the placebo group (table 3).

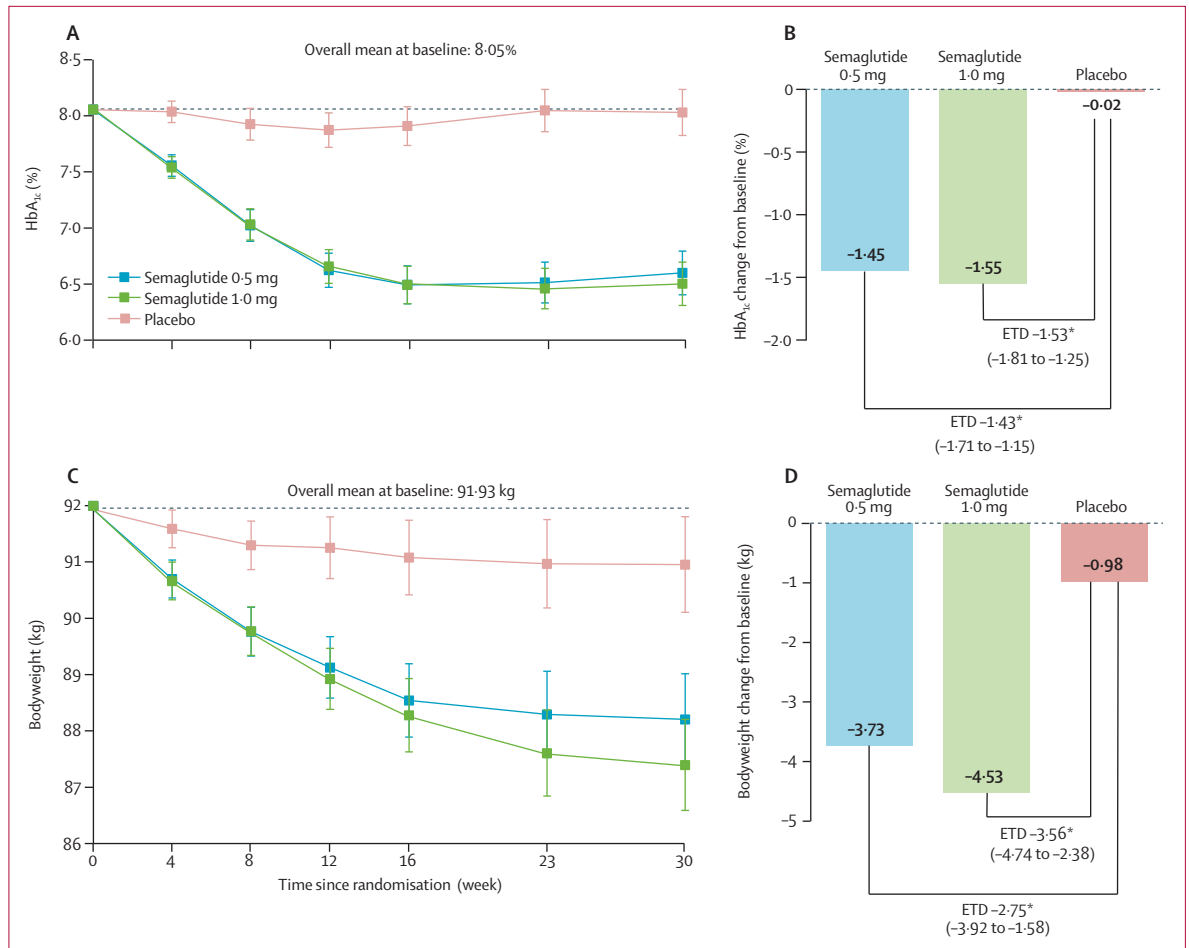BMI and waist circumference were reduced with both doses of semaglutide compared with placebo (table 2);

	0·5 mg semaglutide (n=128)	1·0 mg semaglutide (n=130)	Placebo (n=129)	Total (n=387)
Age (years)	54·6 (11·1)	52·7 (11·9)	53·9 (11·0)	53·7 (11·3)
HbA₁c				
%	8·09 (0·89)	8·12 (0·81)	7·95 (0·85)	8·05 (0·85)
mmol/mol	64·88 (9·74)	65·29 (8·88)	63·43 (9·28)	64·54 (9·31)
Diabetes duration (years)	4·81 (6·10)	3·62 (4·88)	4·06 (5·48)	4·18 (5·52)
Bodyweight (kg)	89·81 (22·96)	96·87 (25·59)	89·05 (22·16)	91·93 (23·83)
BMI (kg/m²)	32·46 (7·62)	33·92 (8·43)	32·40 (6·86)	32·93 (7·68)
eGFR (MDRD; mL/min per 1·73 m²)	95·91 (26·23)	100·90 (27·74)	100·20 (24·97)	99·02 (26·37)
Sex				
Female	68 (53%)	50 (38%)	59 (46%)	177 (46%)
Male	60 (47%)	80 (62%)	70 (54%)	210 (54%)
Ethnic origin				
Hispanic or Latino	34 (27%)	45 (35%)	36 (28%)	115 (30%)
Not Hispanic or Latino	94 (73%)	85 (65%)	93 (72%)	272 (70%)
Race				
White	83 (65%)	88 (68%)	78 (60%)	249 (64%)
Black or African American	11 (9%)	11 (8%)	9 (7%)	31 (8%)
Asian	26 (20%)	25 (19%)	32 (25%)	83 (21%)

Data are mean (SD) or n (%). eGFR=estimated glomerular filtration rate. MDRD=modification of diet in renal disease. *The modified intention-to-treat population comprised all randomly assigned participants who were exposed to at least one dose of study drug.

Table 1: Baseline characteristics of the modified intention-to-treat population*

***Figure 2*: Efficacy outcomes of 0·5 mg and 1·0 mg semaglutide once-weekly, compared with placebo**
Change in mean HbA$_{1c}$ by week (A), mean HbA$_{1c}$ after 30 weeks (B), change in mean bodyweight by week (C), and mean bodyweight after 30 weeks (D). *Indicates significance (p value <0·0001). Values are estimated means (95% CI) from a mixed model for repeated measurements analysis using on-treatment without rescue medication data from the modified intention-to-treat population.

however, total cholesterol, LDL-cholesterol, and free fatty acids were significantly reduced with 1·0 mg semaglutide only, compared with placebo. No significant between-group differences were noted for HDL-cholesterol, triglycerides, VLDL-cholesterol (appendix) or changes in blood pressure (table 2).

No deaths were reported in any of the groups. The proportion of participants reporting any adverse events was higher with semaglutide 0·5 mg versus placebo, whereas the number of reported serious adverse events was broadly similar between all groups (table 4, appendix). Most reported adverse events were of mild or moderate severity (table 4). The proportion of participants prematurely discontinuing treatment because of adverse events was 6% for 0·5 mg semaglutide, 5% for 1·0 mg semaglutide, and 2% for placebo (appendix).

The most frequent adverse events in the semaglutide groups were gastrointestinal in nature, and these were also responsible for most of the adverse events leading to premature treatment discontinuation (table 4). Nausea

was reported by 26 (20%) participants who received 0·5 semaglutide, 31 (24%) who received 1·0 mg semaglutide and ten (8%) who received placebo. Reports of nausea were noted to decrease over time in all groups (appendix). Vomiting was reported by five (4%) participants who received 0·5 semaglutide, nine (7%) participants who received 1·0 mg semaglutide, and two (2%) in the placebo group. Diarrhoea was reported by 16 (13%) participants who received 0·5 semaglutide, 14 (11%) who received 1·0 mg semaglutide, and three (2%) who received placebo. Most gastrointestinal adverse events were mild to moderate (table 4).

No episodes of severe or blood glucose-confirmed hypoglycaemia were reported in either semaglutide group; three events were reported in two participants (2%) in the placebo group. All three events occurred after the first dose of rescue medication. No episodes of pancreatitis were reported in the trial. Lipase and amylase concentrations significantly increased with 0·5 mg and 1·0 mg semaglutide, compared with a decrease with

	0·5 mg semaglutide (n=128)			1·0 mg semaglutide (n=130)			Placebo (n=129)
	Change from baseline at week 30 (95% CI)	Estimated treatment difference vs placebo (95% CI)	p value	Change from baseline at week 30 (95% CI)	Estimated treatment difference vs placebo (95% CI)	p value	Change from baseline at week 30 (95% CI)
Glycaemia endpoints							
Mean HbA$_{1c}$ (%)	–1·45 (–1·65 to –1·26)	–1·43 (-1·71 to 1·15)	<0·0001	–1·55 (–1·74 to –1·36)	–1·53 (–1·81 to –1·25)	<0·0001	–0·02 (–0·23 to 0·18)
Mean HbA$_{1c}$ (mmol/mol)	–15·90 (–18·03` to –13·77)	–15·63 (–18·72 to –12·53)	<0·0001	–16·96 (–19·06 to –14·86)	–16·69 (–19·77 to –13·61)	<0·0001	–0·27 (–2·51 to 1·96)
Mean FPG (mmol/L)	–2·51 (–2·87 to –2·14)	–1·96 (–2·49 to –1·43)	<0·0001	–2·34 (–2·70 to –1·98)	–1·79 (–2·31 to –1·26)	<0·0001	–0·55 (–0·94 to –0·16)
Seven-point SMPG (mmol/L)							
Mean	–2·35 (–2·69 to –2·01)	–1·68 (–2·18 to –1·18)	<0·0001	–2·65 (–2·98 to –2·32)	–1·99 (–2·48 to –1·50)	<0·0001	–0·67 (–1·03 to –0·31)
Increment	–0·75 (–1·06 to –0·44)	–0·41 (–0·87 to 0·05)	0·0807	–1·08 (–1·38 to –0·78)	–0·74 (–1·19 to –0·29)	0·0014	–0·34 (–0·68 to –0·003)
Bodyweight endpoints							
Mean bodyweight (kg)	–3·73 (–4·54 to –2·91)	–2·75 (–3·92 to –1·58)	<0·0001	–4·53 (–5·34 to –3·72)	–3·56 (–4·74 to –2·38)	<0·0001	–0·98 (–1·82 to –0·13)
Mean BMI (kg/m²)	–1·36 (–1·65 to –1·07)	–0·98 (–1·40 to –0·56)	<0·0001	–1·61 (–1·89 to –1·32)	–1·23 (–1·65 to –0·82)	<0·0001	–0·38 (–0·68 to –0·08)
Mean waist circumference (cm)	–3·72 (–4·81 to –2·64)	–1·84 (–3·40 to –0·28)	0·0206	–4·06 (–5·14 to –2·98)	–2·18 (–3·74 to –0·61)	0·0066	–1·88 (–3·00 to –0·77)
Blood pressure and pulse rate							
Mean DBP (mm Hg)	–0·50 (–1·79 to 0·80)	–0·89 (–2·81 to 1·02)	0·3586	0·18 (–1·10 to 1·47)	–0·21 (–2·12 to 1·69)	0·8245	0·40 (–1·00 to 1·80)
Mean SBP (mm Hg)	–2·58 (–4·81 to –0·36)	–0·86 (–4·15 to 2·43)	0·6059	–2·74 (–4·95 to –0·54)	–1·03 (–4·29 to 2·24)	0·5369	–1·72 (–4·13 to 0·69)
Mean pulse rate (beats per min)	2·35 (0·83 to 3·87)	2·89 (0·74 to 5·04)	0·0086	2·43 (0·92 to 3·95)	2·97 (0·83 to 5·12)	0·0068	–0·54 (–2·05 to 0·97)

FPG=fasting plasma glucose. SMPG=self-monitored plasma glucose. DBP=diastolic blood pressure. SBP=systolic blood pressure. All p values are two-sided for the null-hypothesis of no treatment difference.

Table 2: **Study endpoints by treatment group**

	0·5 mg semaglutide (n=128)			1·0 mg semaglutide (n=130)			Placebo (n=129)
	Participants achieving target (%)	Odds ratio (95% CI)	p value	Participants achieving target (%)	Odds ratio (95% CI)	p value	Participants achieving target (%)
Treatment targets							
Participants achieving HbA$_{1c}$ targets							
<7·0% (<53 mmol/mol)	95 (74%)	16·92 (8·44 to 33·89)	<0·0001	94 (72%)	15·70 (8·00 to 30·83)	<0·0001	32 (25%)
≤6·5% (≤48 mmol/mol)	76 (59%)	15·99 (7·82 to 32·68)	<0·0001	78 (60%)	18·34 (8·96 to 37·54)	<0·0001	17 (13%)
Participants achieving bodyweight reduction targets							
≥5% reduction	47 (37%)	7·88 (3·65 to 17·04)	<0·0001	58 (45%)	12·01 (5·53 to 26·07)	<0·0001	9 (7%)
≥10% reduction	10 (8%)	3·60 (1·09 to 11·95)	0·0363	17 (13%)	6·23 (1·98 to 19·61)	0·0018	3 (2%)
Participants achieving HbA$_{1c}$ <7·0% without severe or blood-glucose–confirmed hypoglycaemia and without weight gain	85 (66%)	12·69 (6·57 to 24·52)	<0·0001	85 (65%)	12·45 (6·46 to 23·99)	<0·0001	25 (19%)

All p values are two-sided for the null-hypothesis of no treatment difference.

Table 3: **Participants achieving study endpoints by treatment group**

placebo (appendix). Four cases of cholelithiasis were reported: three in participants who received 0·5 mg semaglutide (one categorised as a serious adverse event) and one who received 1·0 mg semaglutide. No cases of cholelithiasis were reported in the placebo group (table 4).

Mean pulse rate increased significantly with both doses of semaglutide compared with placebo by week 30 (table 2). EAC-confirmed neoplasms were reported by five participants treated with 0·5 mg semaglutide, four treated with 1·0 mg semaglutide, and none treated with placebo. These neoplasms included four malignant cases. Single cases of squamous cell carcinoma of skin and breast cancer were confirmed in the 0·5 mg semaglutide group, and single cases of basal cell carcinoma and prostate cancer were confirmed in the 1·0 mg semaglutide group. No cases of pancreatic cancer were reported (table 4). Calcitonin concentrations in both semaglutide groups were consistently low and similar to placebo, and no C-cell abnormalities were noted. 11 participants developed antisemaglutide antibodies; none were observed to exhibit in-vitro neutralising effects on semaglutide or endogenous GLP-1. No clinically relevant changes were noted in other safety laboratory assessments, physical

	0·5 mg semaglutide (N=128)		1·0 mg semaglutide (N=130)		Placebo (N=129)	
	n (%)	Episodes	n (%)	Episodes	n (%)	Episodes
Any adverse events	82 (64%)	364	73 (56%)	269	69 (53%)	224
Serious adverse events	7 (5%)	10	7 (5%)	8	5 (4%)	6
Fatal adverse events	0	··	0	··	0	··
Severe adverse events	9 (7%)	13	8 (6%)	12	4 (3%)	5
Moderate adverse events	35 (27%)	102	31 (24%)	80	26 (20%)	80
Mild adverse events	71 (55%)	249	60 (46%)	177	58 (45%)	139
GI adverse events	49 (38%)	141	50 (38%)	115	19 (15%)	42
Severe	1 (<1%)	1	2 (2%)	2	0	··
Moderate	19 (15%)	33	17 (13%)	35	5 (4%)	11
Mild	38 (30%)	107	41 (32%)	78	16 (12%)	31
Adverse events leading to premature treatment discontinuation	8 (6%)	16	7 (5%)	11	3 (2%)	5
All GI adverse events	5 (4%)	7	4 (3%)	5	1 (<1%)	1
Nausea	2 (2%)	2	2 (2%)	2	1 (<1%)	1
Vomiting	1 (<1%)	1	2 (2%)	2	0	··
Diarrhoea	3 (2%)	3	0	··	0	··
Adverse events by preferred term (in ≥5% of patients)						
Nausea	26 (20%)	44	31 (24%)	46	10 (8%)	12
Diarrhoea	16 (13%)	27	14 (11%)	19	3 (2%)	3
Headache	15 (12%)	43	9 (7%)	18	8 (6%)	13
Lipase increased	8 (6%)	10	5 (4%)	5	5 (4%)	5
Constipation	8 (6%)	9	5 (4%)	5	1 (<1%)	2
Dyspepsia	7 (5%)	13	5 (4%)	5	3 (2%)	3
Nasopharyngitis	6 (5%)	7	6 (5%)	9	7 (5%)	9
Vomiting	5 (4%)	11	9 (7%)	15	2 (2%)	2
Other adverse events						
Pancreatitis	0	··	0	··	0	··
Cholelithiasis	3 (2%)	3*	1 (<1%)	1	0	··
Malignant neoplasms	2 (2%)	2	2 (2%)	2	0	··
Squamous cell carcinoma of the skin	1 (<1%)	1	0	··	0	··
Basal cell carcinoma	0	··	1 (<1%)	1	0	··
Breast cancer	1 (<1%)	1	0	··	0	··
Prostate cancer	0	··	1 (<1%)	1	0	··
Benign neoplasms	3 (2%)	3	2 (2%)	2	0	··

··=not applicable. GI=gastrointestinal. *One serious adverse event

Table 4: Adverse events

examinations, or electrocardiograms. 13 participants had undetectable plasma semaglutide concentrations throughout the trial, indicating that they had not routinely administered the drug. Ten of these participants had been assigned to the 1·0 mg group and several of these had an increase in HbA$_{1c}$, thereby attenuating the mean HbA$_{1c}$ reduction in the 1·0 mg group.

Although decreases in HbA$_{1c}$ occurred in both dose groups of semaglutide, the decrease in HbA$_{1c}$ was consistently more pronounced in the 1·0 mg semaglutide group than in the 0·5 mg group in all prespecified

sensitivity analyses (appendix). The frequent use of rescue medication, particularly in the placebo group, led to data for more than 30% of participants not being included in the placebo group primary analysis. The outcomes of all sensitivity analyses are included in the appendix.

Discussion

In this trial, 0·5 mg and 1·0 mg semaglutide given once per week for 30 weeks significantly improved glycaemic control and bodyweight in treatment-naive patients with type 2 diabetes, compared with placebo. Nearly three quarters of participants in the semaglutide groups reached the ADA-recommended HbA$_{1c}$ target of less than 7·0%,[12] and almost 60% achieved the American Association of Clinical Endocrinologists (AACE)/National Institute for Health and Care Excellence (NICE) target of 6·5% or less.[2,13] These findings are consistent with observations in an earlier 12-week dose-finding study[14] of semaglutide in 415 participants with type 2 diabetes treated with diet and exercise, with or without a stable metformin regimen, where up to 81% of the participants receiving semaglutide 0·1–1·6 mg achieved an HbA$_{1c}$ concentration of less than 7·0% (up to 63% for the ≤6·5% target).

Because a dose-response was evident in the dose-finding study,[14] it was surprising that no apparent dose-related differences in glycaemic control were evident with semaglutide in this study. However, although both doses produced similar mean HbA$_{1c}$ reductions from baseline, the decrease in HbA$_{1c}$ was consistently more pronounced in the 1·0 mg semaglutide group than in the 0·5 mg semaglutide group in all prespecified sensitivity analyses. A possible explanation for this finding could be that the low mean HbA$_{1c}$ achieved by the end of treatment, and the high percentage of subjects achieving HbA$_{1c}$ readings of less than 7·0%, might have reduced the visibility of a dose-dependent treatment difference in this treatment-naive, type 2 diabetes population. Furthermore, because the sample size was small, the dose–response effect might have been skewed because of the 13 participants who had undetectable plasma semaglutide levels throughout the trial. By contrast with findings for HbA$_{1c}$, weight loss with semaglutide 1·0 mg was numerically higher than for semaglutide 0·5 mg. However, the effects of GLP-1 receptor agonists on glycaemic control and bodyweight appear to be independent,[15] with glycaemic control mainly mediated by pancreatic GLP-1 receptors and weight loss by GLP-1 receptors in the brain.[16–18] This result supports the proposal that glycaemic effects show different dose–response relationships than effects on bodyweight.

In this study, both doses of semaglutide led to significant weight loss, compared with placebo. This is a particularly relevant finding, because many current treatments for diabetes are either weight-neutral or associated with weight gain.[19–21] Current treatment guidelines from ADA/EASD and AACE stress the importance of avoiding weight

gain and minimising the risk of treatment-emergent hypoglycaemia while managing patients with type 2 diabetes. Weight gain and obesity are associated with an increase in the risk of cardiovascular complications[22] and other comorbidities,[23] as well as a reduction in quality of life.[24] Furthermore, weight gain might contribute to patient frustration and an absence of motivation, and lead to reduced compliance with medication.[25] Results from studies also suggest that individuals with type 2 diabetes are reluctant to begin treatments associated with an increased risk of weight gain.[1,26] Even the perception that regular use of diabetes therapy would result in weight gain is associated with a reduced adherence to treatment in individuals with type 2 diabetes.[26]

Although populations and trial durations might be varied, indirect comparisons of the findings from this trial with those from similar monotherapy trials with other GLP-1 receptor agonists indicate that the improvements in glycaemic control and bodyweight are at least similar—and potentially greater—with semaglutide. The proportions of patients achieving the ADA HbA$_{1c}$ target have been reported as 40–49% with albiglutide (30 or 50 mg); 43–51% with liraglutide (1·2 or 1·8 mg); 62–63% with dulaglutide (0·75 or 1·5 mg); and 63% with exenatide extended release (2 mg), compared with 72–74% with semaglutide in this trial.[27–30] Similarly, the magnitude of the change from baseline in bodyweight (–3·73 kg with 0·5 mg semaglutide and –4·53 kg with 1·0 mg semaglutide) was numerically higher than that seen for other GLP-1 receptor agonists (reported at –0·4 to –2·5 kg),[27–30] similar to the weight loss reported with semaglutide in an earlier phase 2 dose-finding study.[14] The high proportion of participants in this trial who achieved the ADA HbA$_{1c}$ target of less than 7·0% without weight gain or hypoglycaemia suggests that semaglutide might potentially ameliorate several of the negative health consequences of type 2 diabetes. Head-to-head trials comparing semaglutide with other GLP-1 receptor agonists are needed to draw firm conclusions about potential differences.

The profile of adverse events with semaglutide was similar to that noted with other GLP-1 receptor agonists,[31] with gastrointestinal adverse events the most frequent. These events were largely mild-to-moderate and led to treatment discontinuation in only a few participants; the frequency of nausea peaked shortly after treatment initiation and diminished over time. Dose escalation has previously been shown to partly ameliorate gastrointestinal adverse events associated with use of GLP-1 receptor agonist,[14] as reflected in the trial design. Although lipase and amylase concentrations increased with semaglutide, there is no evidence of an association with pancreatitis, and no episodes of pancreatitis were reported in this trial.

The modest increase in pulse rate compared with placebo is also in line with findings from studies with other GLP-1 receptor agonists, although the decrease in systolic blood pressure noted with other GLP-1 receptor agonists[32] was not statistically significant in this trial. Additionally, findings from the SUSTAIN 6 trial,[33] designed to assess cardiovascular safety of semaglutide in patients with type 2 diabetes, have shown a significant reduction in cardiovascular risk with semaglutide compared with placebo. The first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke took place in 7% of patients treated with semaglutide 0·5 mg or 1·0 mg and 9% with placebo (hazard ratio 0·74, 95% CI 0·58–0·95; p<0·001 for non-inferiority).[33]

In this trial, more malignant neoplasms were reported in the semaglutide groups, although these were very few (two in each of the semaglutide groups versus none in the placebo groups). However, in the much larger and longer SUSTAIN 6 trial,[33] malignant neoplasms were equally distributed between the semaglutide and placebo groups (hazard ratio 0·94, 95% CI 0·67–1·32), with no apparent differences for any types of malignant neoplasms.

A limitation of this trial was its short duration, which might not have allowed sufficient time for the full effects of semaglutide, on bodyweight in particular, to be assessed. Furthermore, the small sample size might not have had completely balanced baseline characteristics between the groups, as noted for baseline weight and sex distribution. The slightly higher number of overweight men in the 1·0 mg group could have affected the weight-loss results. Results from other phase 3a trials are needed to confirm consistency in the results. Another limitation was the frequent use of rescue medication, which led to missing data in more than 30% of participants in the placebo group. An advantage of this trial design was that use of a volume-matched placebo allowed for masking within each dose for both the clinician and the patient, reducing the risk of bias. GLP-1 receptor agonists are not generally used as monotherapies but are typically started in combination with metformin, which might be another consideration for treatment decisions.[1]

In conclusion, once-weekly semaglutide monotherapy at a dose of 0·5 mg or 1·0 mg in individuals with type 2 diabetes was associated with better glycaemic control and better reductions in bodyweight than placebo. Adverse events were predominantly gastrointestinal effects, and the safety and tolerability profile was consistent with previous observations with other GLP-1 receptor agonists.

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