Napoli Raffaele (Orcid ID: 0000-0002-3366-2321)
Giorgino Francesco (Orcid ID: 0000-0001-7372-2678)

Title page

Title: Once-weekly semaglutide use in patients with type 2 diabetes: real-world data from the SURE Italy observational study

Short running title: Use of once-weekly semaglutide in routine clinical practice in SURE Italy

Authors: Raffaele Napoli,*[1] Cesare Berra,[2] Andrei-Mircea Catarig,[3] Chiara Di Loreto,[4] Emily Donatiello,[5] Tina Landsvig Berentzen,[3] Dario Pitocco,[6] Francesco Giorgino[7]

Author affiliations:

[1]Dept. of Translational Medical Sciences Federico, II University School of Medicine, Napoli, Italy

[2]IRCCS Multimedica, Milan, Italy

[3]Novo Nordisk A/S, Søborg, Denmark

[4]Diabetic Clinic, USL Umbria1, Perugia Territorial Health Structure, Perugia, Italy

[5]Novo Nordisk spa, Rome, Italy

[6]Diabetes Care Unit Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome Italy

[7]Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy

*Corresponding author

Contact details for corresponding author:

Via S. Pansini, 5

Napoli, Italy 80131

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.15020

Phone: +390817463736

napoli@unina.it

Abstract

Aims: SURE Italy, a multicentre, prospective, open-label, observational, real-world study, investigated once-weekly (OW) semaglutide in patients with type 2 diabetes (T2D) in routine clinical practice.

Materials and methods: Adults with T2D and ≥1 documented HbA_{1c} level within 12 weeks of semaglutide initiation were enrolled. The primary endpoint was change in HbA_{1c} from baseline to end of study (EOS; ~30 weeks). Other endpoints included changes in body weight (BW), waist circumference and patient-reported outcomes (PROs), and the proportion of patients achieving HbA_{1c} <7.0% or <6.5%, weight loss ≥5% and a post-hoc composite endpoint (HbA_{1c} reduction of ≥1%-point and weight loss ≥5%). These endpoints were reported for patients on semaglutide at EOS (effectiveness analysis set [EAS]). Safety data were reported in the full analysis set (FAS).

Results: Of 579 patients who initiated semaglutide (FAS), 491 completed the study on treatment (EAS). Mean baseline HbA_{1c} was 8.0%, and 20.7% (120/579) of patients had HbA_{1c} <7.0%. Mean semaglutide dose at EOS was 0.66 ± 0.28 mg. In the EAS, mean HbA_{1c} and BW decreased by 1.1%-point (95% confidence interval [CI] 1.20,1.05; $p<0.0001$) and 4.2 kg (95% CI 4.63,3.67; $p<0.0001$), respectively. At EOS, 61.7% and 40.8% of patients achieved HbA_{1c} <7.0% and <6.5%, respectively, 40.5% achieved weight loss ≥5% and 25.3% achieved the post-hoc composite endpoint. PROs improved from baseline to EOS. No new safety concerns were identified.

Conclusions: In routine clinical practice in Italy, patients with T2D treated with OW semaglutide for 30 weeks achieved clinically significant improvements in HbA_{1c}, BW and other outcomes.

Keywords: *Semaglutide, type 2 diabetes, real-world evidence, GLP-1 analogue, glycaemic control, observational study*

Introduction

Italy has among the highest prevalence of type 2 diabetes (T2D) in Europe, affecting an estimated 4.5 million inhabitants in 2021.[1] This high rate is concerning, as T2D is associated with high morbidity and mortality.[1] In Italy, a significant proportion of patients with T2D are managed in diabetes specialty centres. Over one-third of patients with T2D who attend these centres also have cardiovascular disease (CVD)—defined as atherosclerotic CVD (ASCVD), cerebrovascular disease, coronary heart disease (CHD), peripheral artery disease or carotid artery disease—85% having ASCVD.[2] The treatment goals for T2D, as supported by the American Diabetes Association (ADA) standard of care, the European Association for the Study of Diabetes (EASD) treatment guidelines and the recent ADA/EASD consensus report, are to prevent or delay complications and maintain quality of life through glycaemic control and management of CV and kidney disease risk.[3-5]

The 2021 Italian guidelines for the management and treatment of T2D recommend metformin, sodium–glucose cotransporter-2 inhibitors (SGLT2is) or glucagon-like peptide-1 receptor agonists (GLP-1RAs) as first-line treatment options in patients with T2D and previous CV events (without heart failure).[6,7] Specifically, GLP-1RAs lower CV risk factors, such as blood pressure,[8] and act on inflammation.[9] Yet, few patients in Italy are treated with SGLT2is or GLP-1RAs, in contrast with current national and international guidelines.[2,3,6,7] However, the study presented herein was based on the then-current 2018 Italian guidelines,[10] which recommended GLP-1RAs as second-line therapy after metformin, regardless of patient type.

Semaglutide (Novo Nordisk A/S, Denmark), a human glucagon-like peptide-1 analogue, suitable for once-weekly (OW) subcutaneous (s.c.) administration at doses of 0.5 mg and 1.0 mg, has been approved by many regulatory agencies for treating adults with T2D, in addition to diet and exercise.[11,12] Compared with placebo and many active comparators, OW semaglutide showed superior, clinically relevant reductions in HbA_{1c} and body weight in the SUSTAIN clinical trials, with a similar safety profile as other GLP-

1RAs.[13-18] However, the strict inclusion/exclusion criteria in randomized controlled trials (RCTs) often result in a patient population that does not fully represent patients in routine clinical practice. Real-world (RW) studies, designed to complement the findings of RCTs, are important to understand the use and value of a drug in routine clinical practice.[19] SURE Italy is part of the SURE programme, comprising nine large-scale observational RW studies that investigated OW semaglutide in routine clinical practice in a diverse range of patients with T2D in Canada, Denmark/Sweden, France, Germany, Italy, the Netherlands, Spain, Switzerland and the UK.

Methods

Study design

SURE Italy was a prospective, open-label, observational study of approximately 30 weeks, assessing OW s.c. semaglutide use in adult patients with T2D, treated in routine clinical practice at 38 diabetes specialty centres in Italy. The decision to initiate semaglutide treatment was at the treating physician's discretion and was independent from the decision to include the patient in the study.

Patients were to be treated with OW s.c. semaglutide in a prefilled pen injector, according to routine clinical practice. The treating physician determined the maintenance dose of semaglutide and any subsequent changes to this dose. During the first visit (week 0), informed consent was obtained. This was followed by intermediate visits 2 to 5 (weeks 1 to 27) and an end of study (EOS) visit (visit 6, weeks 28 to 38). Patients only attended the intermediate visits if applicable according to local clinical practice.

The study was conducted in accordance with the Declaration of Helsinki[20] and Guidelines for Good Pharmacoepidemiology Practices,[21] and was approved by the Ethics Committees of the recruiting centres. Patients provided informed written consent before commencement of the study. SURE Italy is registered with ClinicalTrials.gov (trial number NCT04094415).

Study population

Eligible patients were male or female aged ≥18 years with a confirmed diagnosis of T2D and at least one available and documented HbA_{1c} level within 12 weeks prior to inclusion and initiation of semaglutide treatment, respectively. Exclusion criteria included mental incapacity, unwillingness or language barriers precluding adequate understanding of or cooperation with the study, treatment with any investigational drug within 90 days prior to study enrolment, hypersensitivity to semaglutide or to any of the excipients and previously giving informed consent in a SURE study. The first patient visit occurred on 28 October 2019, and the last patient visit occurred on 28 July 2021.

Endpoints

The primary endpoint was change in HbA_{1c} (%-point and mmol/mol) from baseline to EOS (approximately 30 weeks). Secondary endpoints included: change from baseline to EOS in body weight (kg and %) and waist circumference (cm), and the proportion of patients achieving HbA_{1c} <7.5% (59 mmol/mol) or <7.0% (53 mmol/mol) and achieving weight loss ≥3% or ≥5%. Patients experiencing documented and/or severe hypoglycaemia was also a secondary endpoint. Severe hypoglycaemia was defined as an episode of hypoglycaemia requiring assistance from another person to actively administer carbohydrate or glucagon, or take other corrective actions. Additional secondary endpoints were patient-reported outcomes including change from baseline to EOS in Diabetes Treatment Satisfaction Questionnaire status (DTSQs), which provides a measure of how satisfied patients are with their current diabetes treatment, and Short-Form 36 Health Survey version 2 (SF-36®v2) physical summary component (PCS) and mental summary component (MCS) scores, which assess health-related quality of life.

Predefined exploratory endpoints included mean weekly semaglutide and insulin doses at EOS, and glucose-lowering therapy use at EOS. Post-hoc endpoints included an HbA_{1c} reduction of ≥1%-point and weight loss of ≥5%, change from baseline to EOS in triglycerides, cholesterol and blood pressure. The proportion of patients achieving HbA_{1c} <6.5% (48 mmol/mol) or weight loss ≥10% were additional post-hoc endpoints.

Safety, including the secondary endpoint of documented and/or severe hypoglycaemia, was evaluated according to adverse event (AE) reporting by the treating physician. All AEs occurring between obtaining consent and the EOS visit were systematically collected and reported.

Statistical analyses

Descriptive statistics were used to characterize the patient population at the time of semaglutide initiation. Baseline characteristics were described for the full analysis set (FAS), which included all patients who provided signed informed consent and initiated treatment with semaglutide.

Primary analyses of the primary, secondary and exploratory endpoints were performed in the effectiveness analysis set (EAS), which included all patients who completed the study (attended the EOS visit) and were receiving semaglutide at EOS. Secondary analyses of the primary, secondary and exploratory endpoints and safety assessments were performed in the FAS.

The main analysis of the primary endpoint was performed using a crude and adjusted analysis of covariance (ANCOVA) model. The crude model included baseline HbA_{1c} (continuous), and the adjusted model included: HbA_{1c} (continuous), pre-initiation use of GLP-1RAs, pre-initiation use of dipeptidyl peptidase-4 inhibitors (DPP-4is), pre-initiation use of insulins, number of oral anti-diabetes drugs (OADs) used pre-initiation, T2D duration (continuous) (not included in the T2D duration subgroups), age (continuous), body mass index (BMI) (continuous) and sex, excluding patients with missing information on HbA_{1c} at EOS. Analyses of the secondary continuous endpoints were performed similarly to the primary analysis of the primary endpoint, using an ANCOVA model in the EAS.

Sensitivity analyses of change in HbA_{1c} and change in body weight from baseline to EOS were based on the FAS and used a mixed model for repeated measurements for the in-study and on-treatment observation periods. These analyses were performed to assess the impact of missing data in the primary analysis, from which patients were excluded if they had not completed the study, had discontinued treatment or had missing information at EOS.

In post-hoc analyses of the EAS, ANCOVA was used to analyse changes from baseline to EOS in HbA_{1c} and body weight by baseline HbA_{1c} and by baseline BMI, as well as changes from baseline to EOS in triglycerides, cholesterol and blood pressure, in the same manner as the primary endpoint. HbA_{1c} reduction of ≥1%-point and weight loss of ≥5% and the proportion of patients achieving HbA_{1c} <6.5% (48 mmol/mol) or weight loss ≥10% were analysed in the EAS. The results from the primary analysis of the primary endpoint are summarized as number of patients with available values, least-square means estimates for change from baseline and associated two-sided 95% confidence intervals (CIs) and p values corresponding to a two-sided test of no difference vs baseline if not otherwise specified. Data were analysed and presented overall and for subgroups based on previous anti-diabetes medication. The subgroups, selected to better reflect the RW population (differing from the categorization in the initial protocol), were: 'OAD-only', 'GLP-1RA-experienced (± OAD)' and 'insulin ± OAD without GLP-1RA'.

Results

Patient population and baseline characteristics

Of 586 patients providing informed consent, one did not meet eligibility criteria, and six did not initiate semaglutide. The FAS comprised 579 patients (**Figure 1**), of whom 68 discontinued study treatment and 20 had unknown treatment status at EOS; the EAS therefore consisted of 491 patients.

Overall, five patients withdrew from the study, 20 patients were lost to follow-up and six patients did not complete visit 6 within the final visit window. Of the 68 patients (11.7%) who discontinued the study treatment, 37 (6.4%) did so due to unacceptable gastrointestinal intolerability.

One patient was misclassified to the EAS and is counted within the 491 patients (**Supplementary Data**). Overall, 215 (37.1%) and 198 (34.2%) patients made 0 or 1 intermediate visits, respectively. Due to COVID-19 pandemic restrictions, some study visits were conducted via telephone: ten patients (1.6%) for intermediate study visits and seven patients (1.3%) for the EOS visit.

Baseline characteristics for all patients in the FAS and by baseline medication subgroups are outlined in **Table 1**. The overall mean HbA_{1c} level was 8.0%, 120 (20.7%) patients had HbA_{1c} <7.0% and mean diabetes duration was 10.1 years.

The most common conditions in patients' medical histories were hypertension (n=400, 69.1%), dyslipidaemia (n=371, 64.1%) and CHD (n=98, 16.9%) (**Table 1**). The most frequently used anti-diabetes drugs were metformin (84.8%) and basal insulin (25.6%; **Supplementary Table 1**). Among CV medications, the most frequently prescribed treatments were lipid-modifying agents (59.1%), renin-angiotensin system-blocking agents (55.3%) and beta-blockers (30.6%; **Supplementary Table 2**).

Overall, 548 (94.6%) and 27 (4.7%) patients initiated semaglutide on 0.25 mg and 0.5 mg, respectively (**Table 1**). Most patients in each baseline medication subgroup were prescribed the on-label dose-titration starting dose of 0.25 mg semaglutide, of which the 'GLP-1RA-experienced' subgroup had the lowest proportion (82.4%), due to having more patients starting on 0.5 mg (14.1%) or 1 mg semaglutide (3.5%). The most common reasons for initiating OW semaglutide were improving glycaemic control (n=460, 79.4%) and achieving weight reduction (n=433, 74.8%). Other reasons included addressing CV risk factors (n=277, 47.8%) and simplifying current treatment regimen (n=110, 19.0%; **Table 1**).

HbA_{1c}

In the EAS, 481 of 491 patients had available HbA_{1c} values at EOS and were included in the analysis of the primary endpoint. Overall, the estimated mean change from baseline to EOS in HbA_{1c} was −1.1%-point (95% CI −1.20,−1.05; p<0.0001) or −12.3 mmol/mol (95% CI −13.17,−11.49) (**Figure 2A** and **Supplementary Figure 1**). In the subgroups, HbA_{1c} was reduced by 1.3%-point (−14.2 mmol/mol) in the 'OAD-only' subgroup, 0.4%-point (−4.3 mmol/mol) in the 'GLP-1RA-experienced' subgroup, and 1.1%-point (−12.4 mmol/mol) in the 'insulin ± OAD without GLP-1RA' subgroup (**Figure 2A**). Results were similar in the sensitivity analyses evaluating the influence of patients who did not complete the study, had missing HbA_{1c} data at EOS or had discontinued treatment.

In the EAS, at EOS 61.7% of patients achieved HbA_{1c} <7%, 77.6% achieved HbA_{1c} <7.5% and 40.8% achieved HbA_{1c} <6.5% (post-hoc analysis) (**Figure 3A**).

In the EAS, mean HbA_{1c} significantly decreased from baseline to EOS across all baseline HbA_{1c} levels: −0.2, −0.9 and −3.1%-point for the <7, ≥7–≤9 and >9% baseline HbA_{1c} subgroups, respectively (**Supplementary Table 3**). Similarly, HbA_{1c} declined significantly by 1.1 to 1.2%-point in all subgroups by baseline BMI (**Supplementary Table 3**).

Body weight and waist circumference

Overall, in the EAS, the estimated mean change in body weight from baseline to EOS was −4.2 kg (95% CI −4.63,−3.67; p<0.0001) (**Figure 2B**). Significant decreases in body weight were observed across the 'OAD-only' (−5.1 kg), 'GLP-1RA-experienced' (−2.2 kg) and 'insulin ± OAD without GLP-1RA' (−2.7 kg) subgroups. Sensitivity analyses supported these results. In the EAS, 57.0% of patients achieved weight loss ≥3% and 40.5% achieved weight loss ≥5%; 13.6% achieved weight loss ≥10% (post-hoc analysis) (**Figure 3B**). When categorized by baseline BMI, all subgroups experienced statistically significant decreases in body weight: −2.6, −4.9 and −6.2 kg for the ≤30, >30–≤35 and >35 kg/m^2 baseline BMI subgroups, respectively (**Supplementary**

Table 3). Body weight also decreased significantly by 4.1 to 4.3 kg across all baseline HbA_{1c} subgroups (**Supplementary Table 3**).

In the EAS, overall change in waist circumference from baseline to EOS was –4.6 cm (95% CI –5.24,–3.91; p<0.0001) (**Figure 2C**). Significant reductions in waist circumference were observed across the 'OAD-only' (–5.2 cm), 'GLP-1RA-experienced' (–2.5 cm) and 'insulin ± OAD without GLP-1RA' (–2.7 cm) subgroups at EOS.

Post-hoc analysis of composite endpoint

The proportion of patients who achieved reduction of HbA_{1c} of ≥1.0%-point and body weight loss of ≥5.0% was 25.3% (**Figure 3C**).

Patient- and physician-reported outcomes

In the EAS, SF-36®v2 PCS and MCS scores improved from baseline to EOS by 2.4 (95% CI 1.84,2.95; p<0.0001) and 2.4 (95% CI 1.70,3.12; p<0.0001), respectively (**Supplementary Figure 2A and B**). Similar statistically significant improvements were observed for all treatment subgroups for the PCS and MCS, except in the 'GLP-1RA-experienced' subgroup for the SF-36®v2 PCS. Overall, in the EAS, the estimated mean change from baseline to EOS in DTSQs score was 6.8 points (95% CI 6.30,7.32; p<0.0001) (**Supplementary Figure 2C**).

Clinical success in relation to the reason for initiating semaglutide was achieved for 83.9% of patients, as evaluated by the treating physician.

Semaglutide dose EOS

At EOS, 11.4%, 49.3% and 38.3% of patients were taking 0.25, 0.5 and 1.0 mg doses of semaglutide, respectively, with a mean dose of 0.66 ± 0.28 mg (**Supplementary Table 4**).

Insulin and anti-diabetes drug use

The mean (standard deviation [SD]) bolus insulin dose for insulin-using patients in the EAS was 19.9 (9.01) IU/day at baseline and 17.8 (9.50) IU/day at EOS. The mean (SD) basal insulin dose was 21.1 (12.27) IU/day at baseline and 24.1 (14.66) IU/day at EOS (**Table 2**).

In the EAS and FAS, the percentages of patients who used DPP-4is, SGLT2is, GLP-1RAs, sulphonylureas and bolus insulin were lower at EOS compared with baseline (**Table 2** and **Supplementary Table 1**).

Laboratory parameters and blood pressure

Significant decreases in triglycerides (–29.9 mg/dL), low-density lipoprotein cholesterol (–14.5 mg/dL) and total cholesterol (–17.1 mg/dL) from baseline to EOS were reported ($p<0.0001$ for all). Systolic and diastolic blood pressure also decreased significantly from baseline to EOS ($p<0.0001$ for both) (**Supplementary Table 5**).

Safety

Overall, 143 AEs were reported in 81 patients in the FAS during the study regardless of semaglutide treatment status (**Supplementary Table 6**); 129 events were considered non-serious, of which 79 were gastrointestinal. Thirteen patients (2.2%) in the FAS reported 14 serious AEs, four of which were cardiac disorders. Further, 60 AEs in 35 patients (6.0% of the FAS) led to permanent semaglutide discontinuation: two serious AEs in two patients and 58 non-serious AEs in 33 patients.

Severe or documented hypoglycaemic episodes were experienced by five patients (0.9%; 11 events) in the FAS (**Supplementary Table 6**) and two patients (0.4%; four events) in the EAS.

Discussion

SURE Italy is part of the SURE programme and represents the first large-scale RW study of OW semaglutide use in Italy in a diverse population of adults with T2D. Patients treated with OW semaglutide during this study achieved clinically relevant improvements in HbA_{1c}, body weight and waist circumference and showed improvements in most patient-reported outcomes, in the total population and across all baseline medication subgroups. Improvements in HbA_{1c} were observed in all baseline HbA_{1c} subgroups, the extent of which correlated positively with baseline HbA_{1c} level (i.e., patients with higher baseline levels experienced greater reductions). Improvements in body weight were also seen in all baseline BMI categories, and those with higher baseline BMI experienced greater decreases in body weight. The 6.4% rate of treatment discontinuation due to gastrointestinal intolerability in this RW study was consistent with that seen in OW semaglutide clinical trials.[12]

Glycaemic control was achieved without hypoglycaemia or weight gain, aligning with the 2021 Italian guideline objectives to reduce HbA_{1c} as quickly as possible while minimising risk to patients.[6,22] The results of SURE Italy are consistent with efficacy and safety data from the SUSTAIN RCTs[13-18] and the SURE studies in Canada,[23] Denmark/Sweden,[24] Spain,[25] Switzerland[26] and the UK[27] and pooled analyses of these studies,[28] the latter of which showed that OW semaglutide use in routine clinical practice was associated with clinically relevant improvements in glycaemic control (–0.2 to –2.5%-point) and body weight (–2.5 to –5.6 kg) and was well tolerated in a wide range of adults with T2D. Regional, small and retrospective RW observational studies of semaglutide in clinical practice in Italy have shown similar results,[29-33] increasing the body of evidence for the benefits of OW semaglutide treatment in adults with T2D in RW settings. Moreover, as reported by Di Dalmazi et al., semaglutide was associated with greater reductions in HbA_{1c} and weight versus the maximum doses of OW exenatide and dulaglutide that are available in Italy.[31]

A strength of SURE Italy is its inclusion of a RW population of patients with T2D that is more diverse than those typically enrolled in RCTs. Patients with a wide range of baseline characteristics and baseline medications were included. SURE Italy also included patients using a GLP-1RA at enrolment who then switched to OW semaglutide; in contrast, the SUSTAIN programme did not include GLP-1RA–experienced patients,[13-18] highlighting the complementary value of RW studies. As seen in RW studies, switching from another GLP-1RA to semaglutide provides additional benefits in glycaemic control and body weight.[28] Similarly, in SURE Italy, 'GLP-1RA–experienced' patients had significant reductions in HbA_{1c}, body weight and waist circumference when treated with OW semaglutide, although the reductions were lower versus the total population. This pattern was also observed in REALISE-DM[34] and SURE Canada.[23] Similar results were observed in previous retrospective, observational RW studies of OW semaglutide in Italy.[29,31] Collectively, these data suggest that switching from another GLP-1RA to OW semaglutide confers additional clinical benefits to patients with T2D.

OW semaglutide can be administered with other anti-diabetes drugs.[12] However, discontinuation of DPP-4i treatment is recommended when adding GLP-1RA, due to overlapping mechanisms of action.[35] DPP-4is block DPP-4 from degrading GLP-1, increasing endogenous levels of GLP-1, whereas GLP-1RAs mimic the stimulatory effects of GLP-1.[36] At the beginning of SURE Italy, 13.2% of patients were taking a DPP-4i, decreasing to 1.0% at EOS, demonstrating that most patients stopped DPP-4i treatment after semaglutide initiation, as recommended in the study protocol and guidelines.[35]

While the addition of semaglutide has been associated with a decrease in insulin dose in previous studies,[17,24,37] in this study, there was no change in the total insulin dose by EOS (24.9 IU vs 24.5 IU at baseline), although there were changes in insulin usage (e.g. 21 participants stopping bolus insulin). Factors that may have contributed to this were the submaximal semaglutide doses, lack of deintensification of insulin due to the absence of structured algorithms for insulin titration/reduction, and higher fasting plasma glucose and HbA_{1c} indicating poor glycaemic control at baseline, particularly for those who entered the study on insulin. Despite this, the level of hypoglycaemia remained low. Further, despite a reduction in the percentage of patients using sulphonylureas over our study, 8.6% remained on them at EOS, likely due to treatment inertia, as seen in SURE Switzerland[26] and UK;[27] which may have been further exacerbated by the impact of the COVID-19 pandemic.

Notably, Italian clinical practice differs from that of other countries in the SURE programme in that only diabetes specialists could prescribe anti-diabetes drugs at the time the study was performed; with the release of Nota 100[38] in May 2022, anti-diabetes drugs can now be prescribed by all specialists of the Italian national health system and by general practitioners, depending on the region. Additionally, due to COVID-19 restrictions in Italy during the study, there were fewer intermediate and follow-up visits than anticipated. Some study visits occurred by telephone instead of in person. It is possible that reduced clinic visits during the COVID-19 pandemic impacted T2D management. For example, the mean semaglutide dose at EOS was 0.66 mg, and only 38% of patients in the study achieved a semaglutide dose of 1.0 mg at EOS. This could have been influenced by reductions in clinic visits and highlights the need to help patients reach a 1.0 mg dose in the RW setting. Despite the low dose of semaglutide, valuable clinically relevant results were achieved in SURE Italy.

SURE Italy had several potential limitations.[19] The data were collected during routine clinical practice rather than through mandatory assessment at prespecified time points, which might have affected the robustness and completeness of the dataset. The study was one-armed with no active comparator, and the analyses were based on the EAS. In addition, clinical practice and local guidelines[6,7] changed after the study commenced, which should be considered in the interpretation of the results and the use of OW semaglutide in clinical practice in Italy. For example, the reduction in SGLT2i use might be attributed to the inability to prescribe semaglutide to anyone on an SGLT2i at the time of this study due to lack of reimbursement.

In conclusion, in routine clinical practice in Italy, patients with T2D treated with OW semaglutide achieved clinically significant improvements in glycaemic control, body weight and patient-reported outcomes. The additional benefits on blood pressure and plasma lipid profile are particularly salient, given that they represent major CV risk factors.[39] Patients switching from another GLP-1RA to OW semaglutide also experienced improvements in HbA_{1c} and body weight, despite previous treatment with an agent from the same class. In this RW study, OW semaglutide use was associated with positive clinical benefits, good tolerability and the absence of new safety concerns.

Acknowledgements

This study was funded by Novo Nordisk A/S. Investigating physicians were reimbursed for time spent on documentation and to support data collections and the running of the study. We thank the investigators in this study: Marco Mirani (Rozzano), Valentina Todisco (Brindisi), Francesco Manetti (Firenze), Luciano Zenari (Negrar), Gerardo Corigliano (Napoli), Maria Calabrese (Prato), Olga Disoteo (Milano), Carlo Giorda (Chieri), Carmine Gazzaruso (Vigevano), Gianluigi Vendemiale (Foggia), Uberto Pagotto (Bologna), Enrico Torre (Genova), Antonella Marino (Casarano), Franco Cavalot (Orbassano), Antonio Belviso (Brembate di Sopra), Fabrizio Querci (Alzano Lombardo), Simona Frontoni (Roma), Raffaella Buzzetti (Roma), Elisa Forte (Gaeta), Alberto Marangoni (Bassano Del Grappa VI), Franco Grimaldi (Udine), Michele Cutolo (Poggiomarino), Francesca Pellicano (Ravenna), Gabriele Brandoni (Macerata), Andrea Girola (Garbagnate Milanese), Pasquale De Cata (Pavia), Marco Strazzabosco (Vicenza), Silvio Settembrini (Napoli), Graziano Di Cianni (Livorno), Pasquale Alfidi (Avezzano), Luigi Puccio (Catanzaro), Agostino Paccagnella (Treviso), Vincenzo Cimino (Milano). We also thank all the participants and study-site staff, as well as Sanskruti Jayesh Patel and Nick Fabrin Nielsen from Novo Nordisk for their review and input to the manuscript, and Sam Brown (AXON Communications) for medical writing and editorial assistance (funded by Novo Nordisk A/S).

Conflicts of interest

A-M.C. is an employee of Novo Nordisk and owns stock in the company. E.D. is an employee of Novo Nordisk. T.L.B. is an employee of Novo Nordisk and owns stock in the company. F.G. has received grants from Eli Lilly and Roche Diabetes Care; consulting fees and/or honoraria for membership on advisory boards from AstraZeneca, Eli Lilly, Novo Nordisk, Roche Diabetes Care, Sanofi, Boehringer Ingelheim, Lifescan, Merck Sharp & Dohme, Medimmune and Medtronic; and lecture and other fees from AstraZeneca, Eli Lilly, Novo Nordisk, Roche Diabetes Care and Sanofi.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th Edition. https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf. Accessed November 15, 2022.
2. Russo GT, Corigliano G, Arturi F, Cavallo MG, Bette C, Mannucci E. CAPTURE: A cross-sectional study on the prevalence of cardiovascular disease in adults with type 2 diabetes in Italy. *Nutr Metab Cardiovasc Dis.* 2022;32(5):1195-1201.
3. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2022;45(11):2753-2786.
4. ElSayed NA, Aleppo G, Aroda VR, et al. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2023. *Diabetes Care.* 2022;46(Supplement_1):S49-S67.
5. ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2023. *Diabetes Care.* 2022;46(Supplement_1):S158-S190.
6. Mannucci E, Candido R, Monache LD, et al. Italian guidelines for the treatment of type 2 diabetes. *Acta Diabetol.* 2022;59(5):579-622.
7. Italian Society of Diabetology and Association of Diabetologists. Guidelines of the SID and AMD. Therapy of diabetes mellitus type 2. https://snlg.iss.it/wp-content/uploads/2021/07/LG_379_diabete_2.pdf. Accessed November 14, 2022.
8. Berra C, Manfrini R, Regazzoli D, et al. Blood pressure control in type 2 diabetes mellitus with arterial hypertension. The important ancillary role of SGLT2-inhibitors and GLP1-receptor agonists. *Pharmacol Res.* 2020;160:105052.
9. Bendotti G, Montefusco L, Lunati ME, et al. The anti-inflammatory and immunological properties of GLP-1 receptor agonists. *Pharmacol Res.* 2022;182:106320.

10. Associazione Medici Diabetologi. Standard Italiani per la cura del diabete mellito 2018. https://aemmedi.it/wp-content/uploads/2009/06/AMD-Standard-unico1.pdf. Accessed September 19, 2022.
11. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem.* 2015;58(18):7370-7380.
12. Novo Nordisk A/S. Ozempic summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/ozempic-epar-product-information_en.pdf. Accessed November 14, 2022.
13. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care.* 2018;41(2):258-266.
14. Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol.* 2017;5(5):341-354.
15. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol.* 2017;5(5):355-366.
16. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol.* 2018;6(4):275-286.
17. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *The Journal of clinical endocrinology and metabolism.* 2018;103(6):2291-2301.
18. Sorli C, Harashima SI, Tsoukas GM, et al. 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. *Lancet Diabetes Endocrinol.* 2017;5(4):251-260.
19. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and impact of real-world clinical data for the practicing clinician. *Adv Ther.* 2018;35(11):1763-1774.
20. World Medical Association. World Medical Assocation Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(20):2191-2194.
21. ISPE. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf.* 2008;17(2):200-208.
22. Italian Society of Diabetology and Association of Diabetologists. Guidelines of the SID and AMD. Therapy of diabetes mellitus type 2. Accessed November 14 hwsi. In.
23. Yale JF, Catarig AM, Grau K, et al. Use of once-weekly semaglutide in patients with type 2 diabetes in routine clinical practice: Results from the SURE Canada multicentre, prospective, observational study. *Diabetes Obes Metab.* 2021;23(10):2269-2278.
24. Rajamand Ekberg N, Bodholdt U, Catarig AM, et al. Real-world use of once-weekly semaglutide in patients with type 2 diabetes: Results from the SURE Denmark/Sweden multicentre, prospective, observational study. *Prim Care Diabetes.* 2021;15(5):871-878.
25. Bellido V, Abreu Padín C, Catarig AM, Clark A, Barreto Pittol S, Delgado E. Once-weekly semaglutide use in patients with type 2 diabetes: results from the SURE Spain multicentre, prospective, observational study. *J Clin Med.* 2022;11(17):4938.
26. Rudofsky G, Catarig AM, Favre L, et al. Real-world use of once-weekly semaglutide in patients with type 2 diabetes: Results from the SURE Switzerland multicentre, prospective, observational study. *Diabetes Res Clin Pract.* 2021;178:108931.

27. Holmes P, Bell HE, Bozkurt K, et al. Real-world use of once-weekly semaglutide in type 2 diabetes: results from the SURE UK multicentre, prospective, observational study. *Diabetes Ther.* 2021;12(11):2891-2905.
28. Yale JF, Bodholdt U, Catarig AM, et al. Real-world use of once-weekly semaglutide in patients with type 2 diabetes: pooled analysis of data from four SURE studies by baseline characteristic subgroups. *BMJ Open Diabetes Res Care.* 2022;10(2):e002619.
29. Di Loreto C, Minarelli V, Nasini G, Norgiolini R, Del Sindaco P. Effectiveness in real world of once weekly semaglutide in people with type 2 diabetes: glucagon-like peptide receptor agonist naïve or switchers from other glucagon-like peptide receptor agonists: results from a retrospective observational study in Umbria. *Diabetes Therapy.* 2022:1-17.
30. Marzullo P, Daffara T, Mele C, et al. Real-world evaluation of weekly subcutaneous treatment with semaglutide in a cohort of Italian diabetic patients. *J Endocrinol Invest.* 2022;45(8):1587-1598.
31. Di Dalmazi G, Coluzzi S, Baldassarre MPA, et al. Effectiveness and tolerability of once-weekly GLP-1 receptor agonists in clinical practice: a focus on switching between once-weekly molecules in type 2 diabetes. *Front Endocrinol (Lausanne).* 2022;13:892702.
32. Di Folco U, Vallecorsa N, Nardone MR, Pantano AL, Tubili C. Effects of semaglutide on cardiovascular risk factors and eating behaviors in type 2 diabetes. *Acta Diabetol.* 2022;59(10):1287-1294.
33. Basile G, Mirarchi L, Amodeo S, et al. Semaglutide and dulaglutide: comparative effectiveness analysis and disparity in the Regional Therapeutic Plan. *JAMD.* 2022;25:105-111.
34. Jain AB, Kanters S, Khurana R, Kissock J, Severin N, Stafford SG. Real-World Effectiveness Analysis of Switching From Liraglutide or Dulaglutide to Semaglutide in Patients With Type 2 Diabetes Mellitus: The Retrospective REALISE-DM Study. *Diabetes Ther.* 2021;12(2):527-536.
35. Draznin B, Aroda VR, Bakris G, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022;45(Supplement_1):S125-S143.
36. Wajchenberg BL. beta-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev.* 2007;28(2):187-218.
37. Kellerer M, Kaltoft MS, Lawson J, et al. Effect of once-weekly semaglutide versus thrice-daily insulin aspart, both as add-on to metformin and optimized insulin glargine treatment in participants with type 2 diabetes (SUSTAIN 11): A randomized, open-label, multinational, phase 3b trial. *Diabetes Obes Metab.* 2022;24(9):1788-1799.
38. Italian Medicines Agency. Nota 100 https://www.aifa.gov.it/documents/20142/1728125/nota-100.pdf. Accessed October 19, 2022.
39. Draznin B, Aroda VR, Bakris G, et al. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2022. *Diabetes Care.* 2022;45(Suppl 1):S144-S174.

Tables

Table 1. Patient demographics and baseline characteristics (FAS).

Characteristic	OAD-only (n=367)	GLP-1RA (n=85)	Insulin ± OAD without GLP-1RA (n=115)	No anti-diabetes drug (n=12)	Total (N=579)
Age, years	61.7 (10.00)	62.6 (8.36)	64.3 (11.29)	62.3 (6.30)	62.4 (10.02)
Female, n (%)	138 (37.6)	38 (44.7)	48 (41.7)	5 (41.7)	229 (39.6)
Baseline HbA_{1c}, %	7.9 (1.40)	7.7 (1.28)	8.4 (1.60)	8.2 (1.54)	8.0 (1.44)
Baseline HbA_{1c}, mmol/mol	63.0 (15.30)	60.4 (14.01)	68.1 (17.45)	65.9 (16.81)	63.7 (15.75)
Fasting plasma glucose, mg/dL	163.2 (49.21)	145.3 (39.15)	165.3 (61.55)	190.8 (15.63)	161.4 (51.93)
Body weight, kg	93.7 (18.93)	94.1 (17.91)	90.7 (19.11)	92.5 (19.18)	93.2 (18.75)
Body mass index, kg/m^2	33.2 (6.20)	33.8 (5.65)	32.2 (5.96)	33.6 (5.72)	33.1 (6.06)
Waist circumference, cm	111.7 (13.39)	113.9 (12.59)	110.1 (13.99)	115.9 (6.70)	111.8 (13.32)
Diabetes duration, years	9.0 (7.05)	12.1 (6.86)	12.6 (8.60)	6.1 (9.17)	10.1 (7.57)
eGFR, mL/min/1.73 m^2	83.8 (19.55)	78.5 (22.69)	77.6 (21.11)	79.1 (14.74)	81.7 (20.65)
eGFR, median (IQR), mL/min/1.73 m^2	87.9 (71.6; 96.8)	82.5 (59.8; 95.6)	80.2 (62.0; 90.3)	80.7 (75.7; 84.1)	84.8 (68.4; 95.9)
Diastolic blood pressure, mmHg	81.2 (8.98)	78.1 (8.49)	79.0 (9.80)	79.2 (8.21)	80.3 (9.12)
Systolic blood pressure, mmHg	135.5 (14.90)	133.8 (14.65)	134.3 (14.66)	132.5 (9.65)	135.0 (14.71)
Starting dose of semaglutide, n (%)					
0.25 mg	357 (97.3)	70 (82.4)	109 (94.8)	12 (100.0)	548 (94.6)
0.5 mg	9 (2.5)	12 (14.1)	6 (5.2)	0	27 (4.7)
1.0 mg	1 (0.3)	3 (3.5)	0	0	4 (0.7)

Medical history, n (%)					
Hypertension	255 (69.5)	63 (74.1)	75 (65.2)	7 (58.3)	400 (69.1)
Dyslipidaemia	229 (62.4)	58 (68.2)	76 (66.1)	8 (66.7)	371 (64.1)
Coronary heart disease	53 (14.4)	19 (22.4)	24 (20.9)	2 (16.7)	98 (16.9)
Peripheral vascular disease	25 (6.8)	3 (3.5)	5 (4.3)	0	33 (5.7)
Stroke	8 (2.2)	4 (4.7)	4 (3.5)	1 (8.3)	17 (2.9)
Heart failure	2 (0.5)	4 (4.7)	3 (2.6)	0	9 (1.6)
Diabetes complications, n (%)					
Diabetic retinopathy	22 (6.0)	6 (7.1)	18 (15.8)	0	46 (8.0)
Diabetic neuropathy	25 (6.8)	8 (9.4)	9 (7.9)	1 (8.3)	43 (7.5)
Diabetic nephropathy	37 (10.1)	18 (21.2)	18 (15.7)	1 (8.3)	74 (12.8)
Reasons to initiate semaglutide, n (%)†					
Improve glycaemic control	301 (82.0)	56 (65.9)	92 (80.0)	11 (91.7)	460 (79.4)
Weight reduction	282 (76.8)	62 (72.9)	80 (69.6)	9 (75.0)	433 (74.8)
Concerns with hypoglycaemia	7 (1.9)	2 (2.4)	15 (13.0)	1 (8.3)	25 (4.3)
Address cardiovascular risk factors	187 (51.0)	25 (29.4)	57 (49.6)	8 (66.7)	277 (47.8)
Simplify current treatment regimen	51 (13.9)	23 (27.1)	36 (31.3)	0	110 (19.0)
Convenience	22 (6.0)	2 (2.4)	4 (3.5)	0	28 (4.8)
Other	5 (1.4)	0	0	0	5 (0.9)

Values are mean (SD) unless otherwise specified. †More than one reason could be chosen.
eGFR, estimated glomerular filtration rate; FAS, full analysis set; GLP-1RA, glucose-like peptide-1 receptor agonist; IQR, interquartile range; OAD, oral anti-diabetes drug; SD, standard deviation.

Table 2. Anti-diabetes drug use at baseline and EOS (EAS).

	OAD-only (n=313)		GLP-1RA (n=78)		Insulin ± OAD without GLP-1RA (n=90)		Total (N=491)	
	Baseline	**EOS**	**Baseline**	**EOS**	**Baseline**	**EOS**	**Baseline**	**EOS**
Metformin	293 (93.6)	283 (90.4)	65 (83.3)	65 (83.3)	65 (72.2)	70 (77.8)	423 (86.2)	422 (85.9)
Sulphonylurea	42 (13.4)	23 (7.3)	10 (12.8)	9 (11.5)	10 (11.1)	10 (11.1)	62 (12.6)	42 (8.6)
OAD combination	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.2)	1 (0.2)
AGI	5 (1.6)	5 (1.6)	4 (5.1)	1 (1.3)	1 (1.1)	2 (2.2)	10 (2.0)	8 (1.6)
Thiazolidinedione	18 (5.8)	13 (4.2)	7 (9.0)	7 (9.0)	3 (3.3)	3 (3.3)	28 (5.7)	23 (4.7)
DPP-4i	50 (16.0)	2 (0.6)	1 (1.3)	0	14 (15.6)	3 (3.3)	65 (13.2)	5 (1.0)
SGLT2i	29 (9.3)	6 (1.9)	3 (3.8)	1 (1.3)	16 (17.8)	2 (2.2)	48 (9.8)	9 (1.8)
GLP-1RA	0	0	78 (100.0)	1 (1.3)	0	0	78 (15.9)	1 (0.2)
Other, excluding insulin	4 (1.3)	3 (1.0)	2 (2.6)	1 (1.3)	0	1 (1.1)	6 (1.2)	6 (1.2)
Basal insulin	0	14 (4.5)	31 (39.7)	31 (39.7)	88 (97.8)	70 (77.8)	119 (24.2)	116 (23.6)

	Mean (SD) total insulin dose (IU)		Number stopped bolus insulin
	Baseline	**EOS**	
Basal insulin (n=119)	21.1 (12.27)	24.1 (14.66)	
Bolus insulin (n=23)	19.9 (9.01)	17.8 (9.50)	
Total insulin (n=121)	24.5 (14.88)	24.9 (15.70)	21

The EAS included patients who attended the EOS visit and were still receiving semaglutide. Total insulin includes bolus, basal and premixed insulin.
AGI, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; EAS, effectiveness analysis set; EOS, end of study; GLP-1RA, glucagon-like peptide-1 receptor agonist; IU, international unit; OAD, oral anti-diabetes drug; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SD, standard deviation.

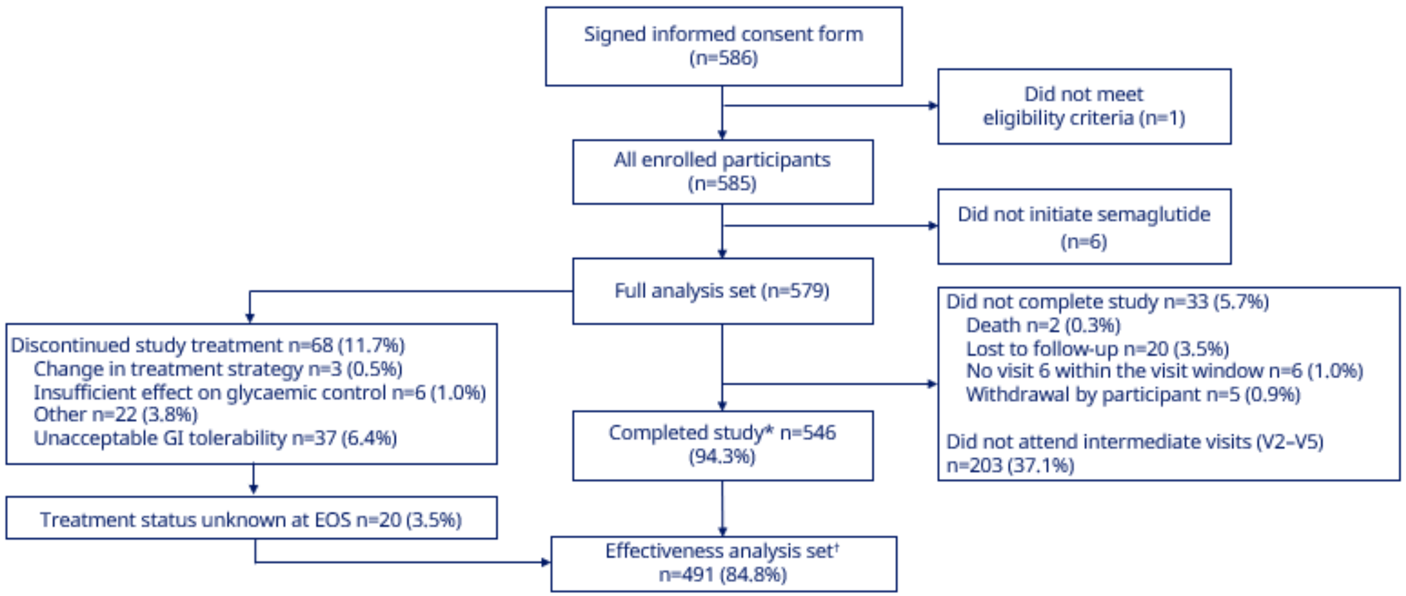
Figure 1. Patient disposition.

Figure 2. Changes in **(A)** HbA_{1c} (% and mmol/mol), **(B)** body weight (kg and %) and **(C)** waist circumference (cm) from baseline to EOS (EAS).

Figure 3. Proportion of patients achieving **(A)** HbA_{1c} targets, **(B)** weight-loss goals and **(C)** HbA_{1c} reduction of ≥1.0%-point and body weight loss of ≥5.0% (EAS).

Figures

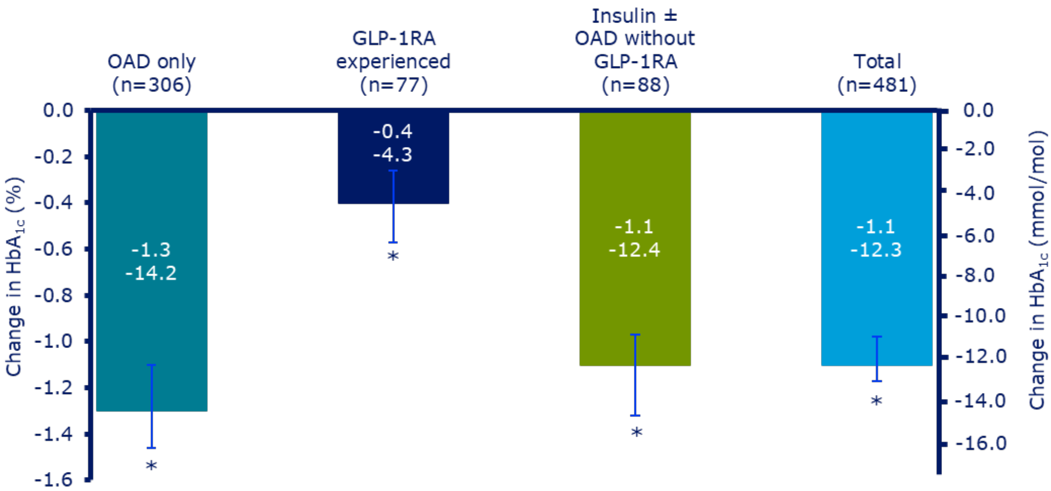
Figure 1. Patient disposition.



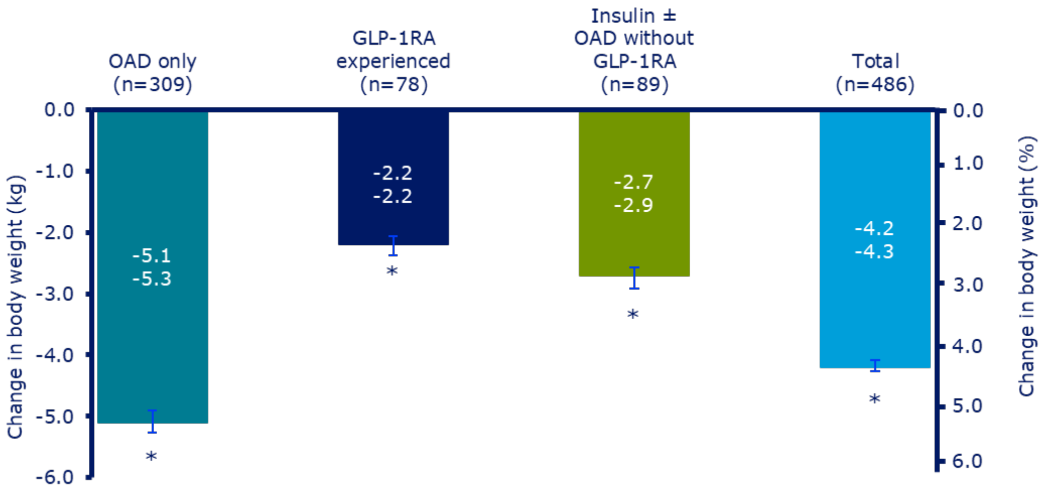
Note: this study was implemented during the lockdown period of the COVID-19 pandemic.
*Patients who initiated the semaglutide treatment and attended the end of study visit. †One patient was misclassified to the EAS and is counted within the n=491 patients.
EAS, effectiveness analysis set; EOS, end of study; GI, gastrointestinal.

Figure 2. Changes in **(A)** HbA_{1c} (% and mmol/mol), **(B)** body weight (kg and %) and **(C)** waist circumference (cm) from baseline to EOS (EAS).

(A)



(B)



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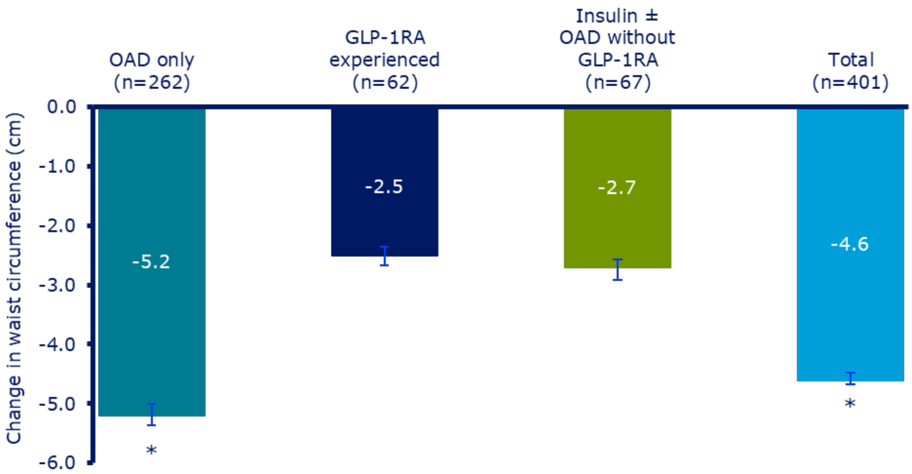
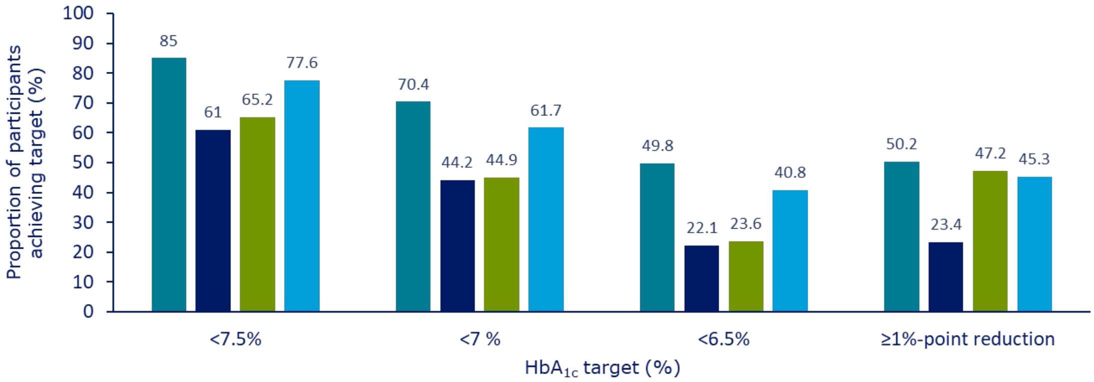


Data are based on the EAS, which included patients who attended the EOS visit and were still receiving semaglutide. n=number of patients with available data.
*p<0.005 for change at EOS vs baseline

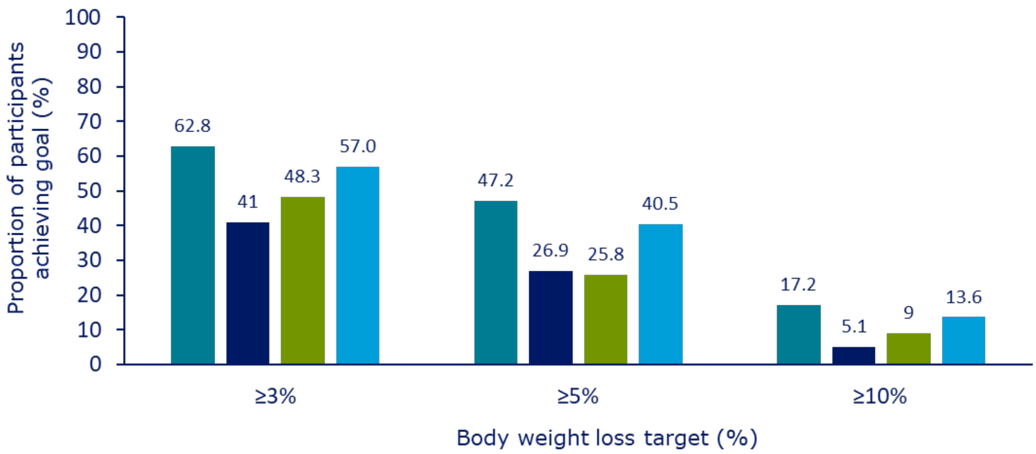
EAS, effectiveness analysis set; EOS, end of study; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral anti-diabetes drug.

Figure 3. Proportion of patients achieving **(A)** HbA_{1c} targets, **(B)** weight-loss goals and **(C)** HbA_{1c} reduction of ≥1.0%-point and body weight loss of ≥5.0% (EAS).

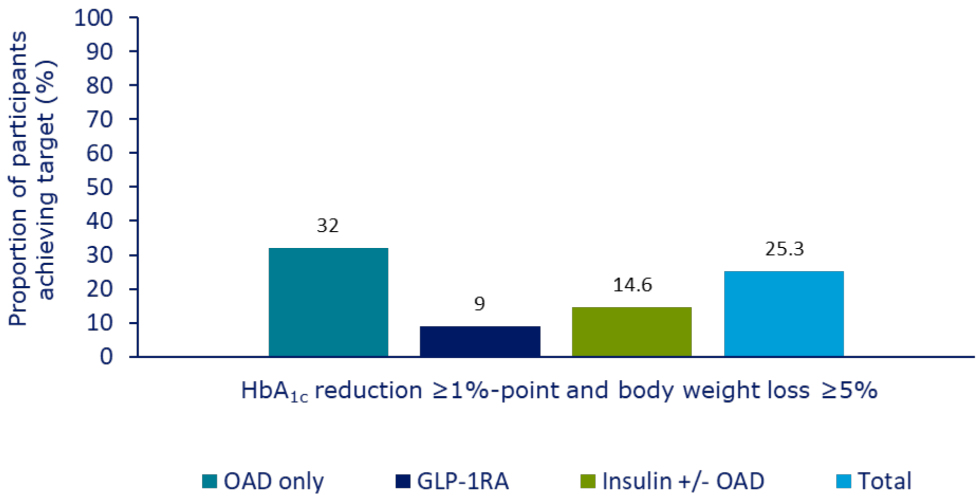
(A)



(B)



(C)



Data are based on the EAS, which included patients who attended the EOS visit and were still receiving semaglutide. n=number of patients with available data.

EAS, effectiveness analysis set; EOS, end of study; GLP-1RA, glucagon-like peptide-1 receptor agonist; OAD, oral anti-diabetes drug.