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

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Abstract

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

Materials and Methods: Adults with T2D and ≥1 documented glycated haemoglobin (HbA1c) level within 12 weeks of semaglutide initiation were enrolled. The primary endpoint was change in HbA1c from baseline to end of study (EOS; ~30 weeks). Other endpoints included changes in body weight, waist circumference and patient-reported outcomes, and the proportion of patients achieving HbA1c <7.0% or <6.5%, weight loss ≥5% and a post-hoc composite endpoint (HbA1c 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.

Results: Of 579 patients who initiated semaglutide (full analysis set), 491 completed the study on treatment (EAS). Mean baseline HbA1c was 8.0%, and 20.7% (120 of 579) of patients had HbA1c <7.0%. Mean semaglutide dose at EOS was 0.66 ± 0.28 mg. In the EAS, mean HbA1c and body weight decreased by 1.1%-point (95% confidence interval 1.20, 1.05; $P < .0001$) and 4.2 kg (95% confidence interval 4.63, 3.67; $P < .0001$), respectively. At EOS, 61.7% and 40.8% of patients achieved HbA1c <7.0% and <6.5%, respectively, 40.5% achieved weight loss ≥5% and 25.3% achieved the post-hoc composite endpoint. Patient-reported outcomes improved from baseline to EOS. No new safety concerns were identified.

Conclusions: In routine clinical practice in Italy, patients with T2D treated with once-weekly semaglutide for 30 weeks achieved clinically significant improvements in HbA1c, body weight and other outcomes.

KEYWORDS

GLP-1 analogue, glycaemic control, observational study, real-world evidence, semaglutide, type 2 diabetes

1 | 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, cerebrovascular disease, coronary heart disease, peripheral artery disease or carotid artery disease), with 85% having atherosclerotic CVD.[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 GLP-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 glycated haemoglobin (HbA1c) 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.

2 | METHODS

2.1 | 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 2-5 (weeks 1-27) and an end of study (EOS) visit (visit 6, weeks 28-38). 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).

2.2 | Study population

Eligible patients were men or women aged ≥18 years with a confirmed diagnosis of T2D and at least one available and documented HbA1c level within 12 weeks before 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 before 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.

2.3 | Endpoints

The primary endpoint was change in HbA1c (%-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 HbA1c <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 the Diabetes Treatment Satisfaction Questionnaire status, 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 HbA1c 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 HbA1c <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.

2.4 | 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 HbA1c (continuous), and the adjusted model included: HbA1c (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 antidiabetes 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 HbA1c 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 HbA1c 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 HbA1c and body weight by baseline HbA1c 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. HbA1c reduction of ≥1%-point and weight loss of ≥5% and the proportion of patients achieving HbA1c <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 versus baseline if not otherwise specified. Data were analysed and presented overall and for subgroups based on previous antidiabetes 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'.

3 | RESULTS

3.1 | 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

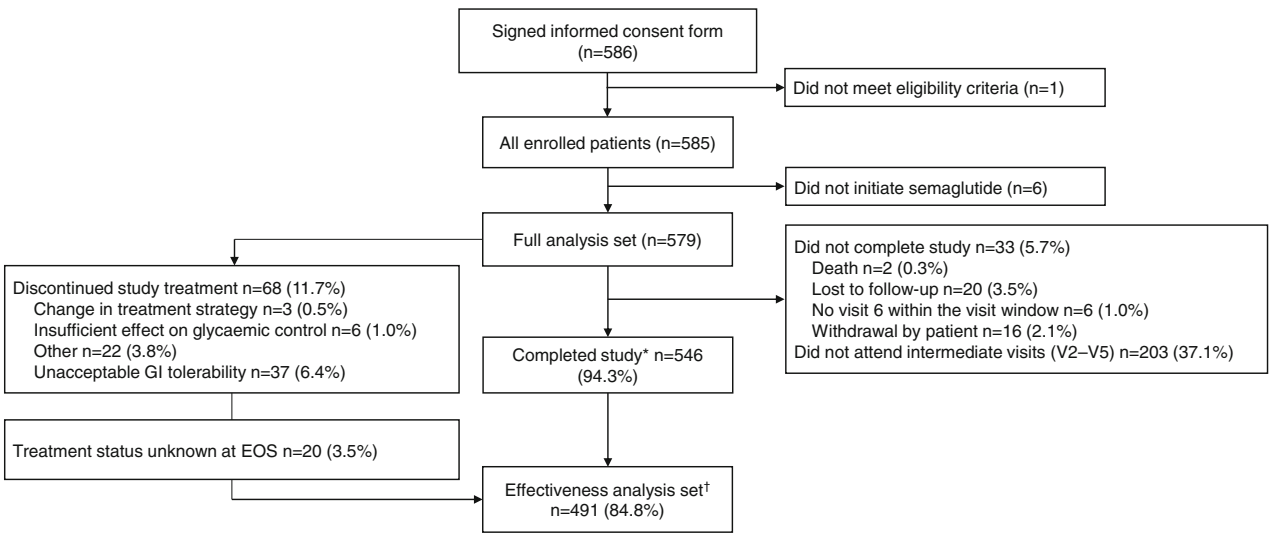

FIGURE 1 Patient disposition. This study was implemented during the lockdown period of the COVID-19 pandemic. *Patients who initiated the semaglutide treatment and attended the end of study visit. †One patient was misclassified to the EAS and is counted within the n = 491 patients. EAS, effectiveness analysis set; EOS, end of study; GI, gastrointestinal

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 were lost to follow-up and six 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 because of unacceptable gastrointestinal intolerability.

One patient was misclassified to the EAS and is counted within the 491 patients (Data S1). Overall, 215 (37.1%) and 198 (34.2%) patients made 0 or 1 intermediate visits, respectively. Because of COVID-19 pandemic restrictions, some study visits were conducted via telephone: 10 patients (1.6%) for intermediate study visits and seven (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

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 antidiabetes 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 HbA1c, %	7.9 (1.40)	7.7 (1.28)	8.4 (1.60)	8.2 (1.54)	8.0 (1.44)
Baseline HbA1c, 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 (%)[a]					
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)

Note: Values are mean (SD) unless otherwise specified.

Abbreviations: eGFR, estimated glomerular filtration rate; FAS, full analysis set; GLP-1RA, glucose-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; IQR, interquartile range; OAD, oral antidiabetes drug; SD, standard deviation.

[a]More than one reason could be chosen.

HbA1c level was 8.0%, 120 (20.7%) patients had HbA1c <7.0% and the 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 coronary heart disease (n = 98, 16.9%) (Table 1). The most frequently used antidiabetes drugs were metformin (84.8%) and basal insulin (25.6%; Table S1). 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%; Table S2).

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%), because of 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

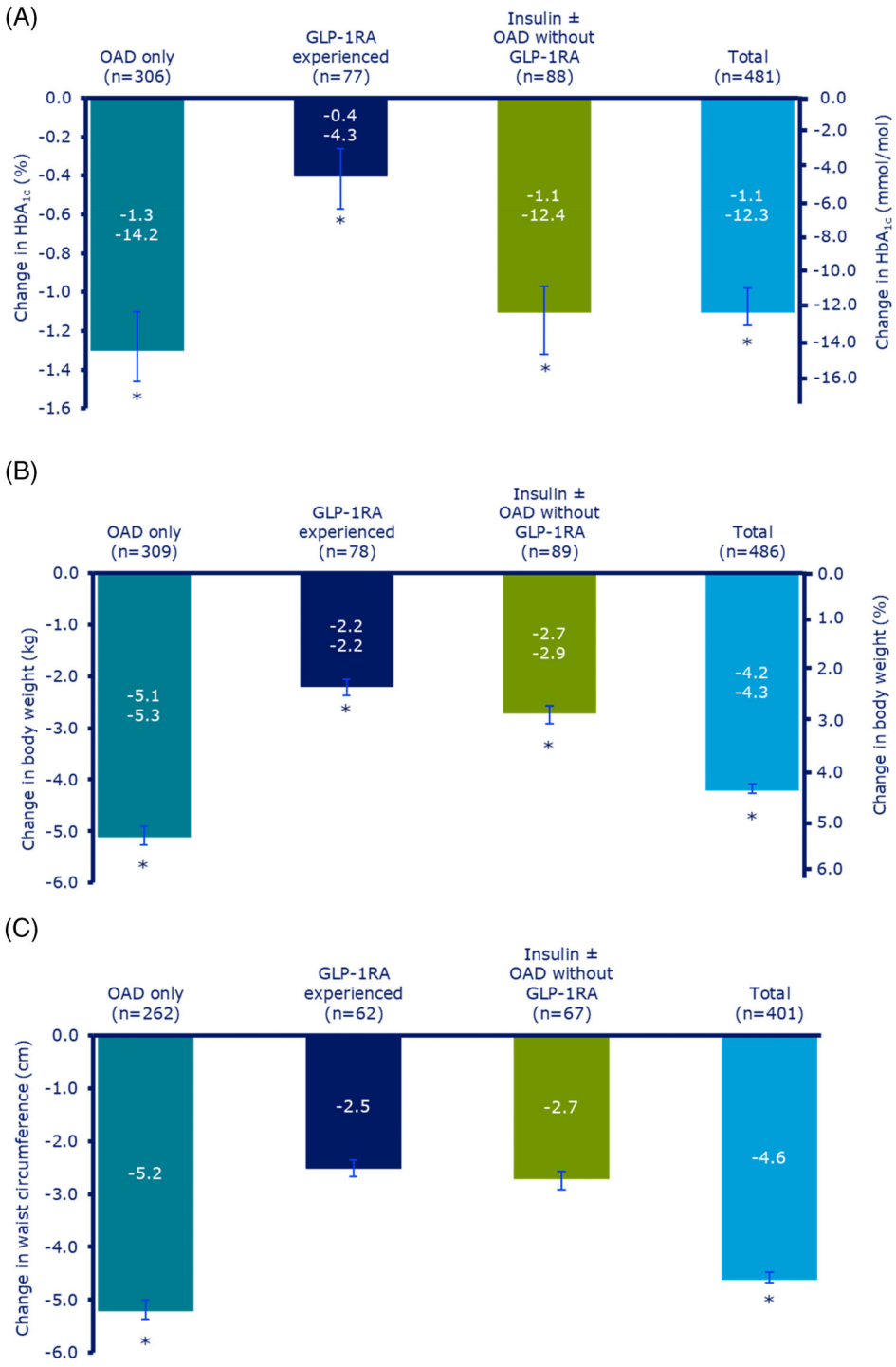

FIGURE 2 Changes in (A) HbA1c (% and mmol/mol), (B) body weight (kg and %) and (C) waist circumference (cm) from baseline to EOS (EAS). Data are based on the EAS, which included patients who attended the EOS visit and were still receiving semaglutide. n = number of patients with available data. *P < .005 for change at EOS versus baseline. EAS, effectiveness analysis set; EOS, end of study; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; OAD, oral antidiabetes drug

addressing CV risk factors (n = 277, 47.8%) and simplifying the current treatment regimen (n = 110, 19.0%; Table 1).

3.2 | Glycated haemoglobin

In the EAS, 481 of 491 patients had available HbA1c values at EOS and were included in the analysis of the primary endpoint. Overall, the estimated mean change from baseline to EOS in HbA1c was −1.1%-point (95% CI −1.20, −1.05; $P < .0001$) or −12.3 mmol/mol (95% CI −13.17, −11.49) (Figure 2A and Figure S1). In the subgroups, HbA1c 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 HbA1c data at EOS or had discontinued treatment.

In the EAS, at EOS 61.7% of patients achieved HbA1c <7%, 77.6% achieved HbA1c <7.5% and 40.8% achieved HbA1c <6.5% (post-hoc analysis) (Figure 3A).

In the EAS, the mean HbA1c significantly decreased from baseline to EOS across all baseline HbA1c levels: −0.2, −0.9 and −3.1%-point for the <7, ≥7–≤9 and >9% baseline HbA1c subgroups, respectively (Table S3). Similarly, HbA1c declined significantly by 1.1 to 1.2%-point in all subgroups by baseline BMI (Table S3).

3.3 | 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; $P < .0001$)

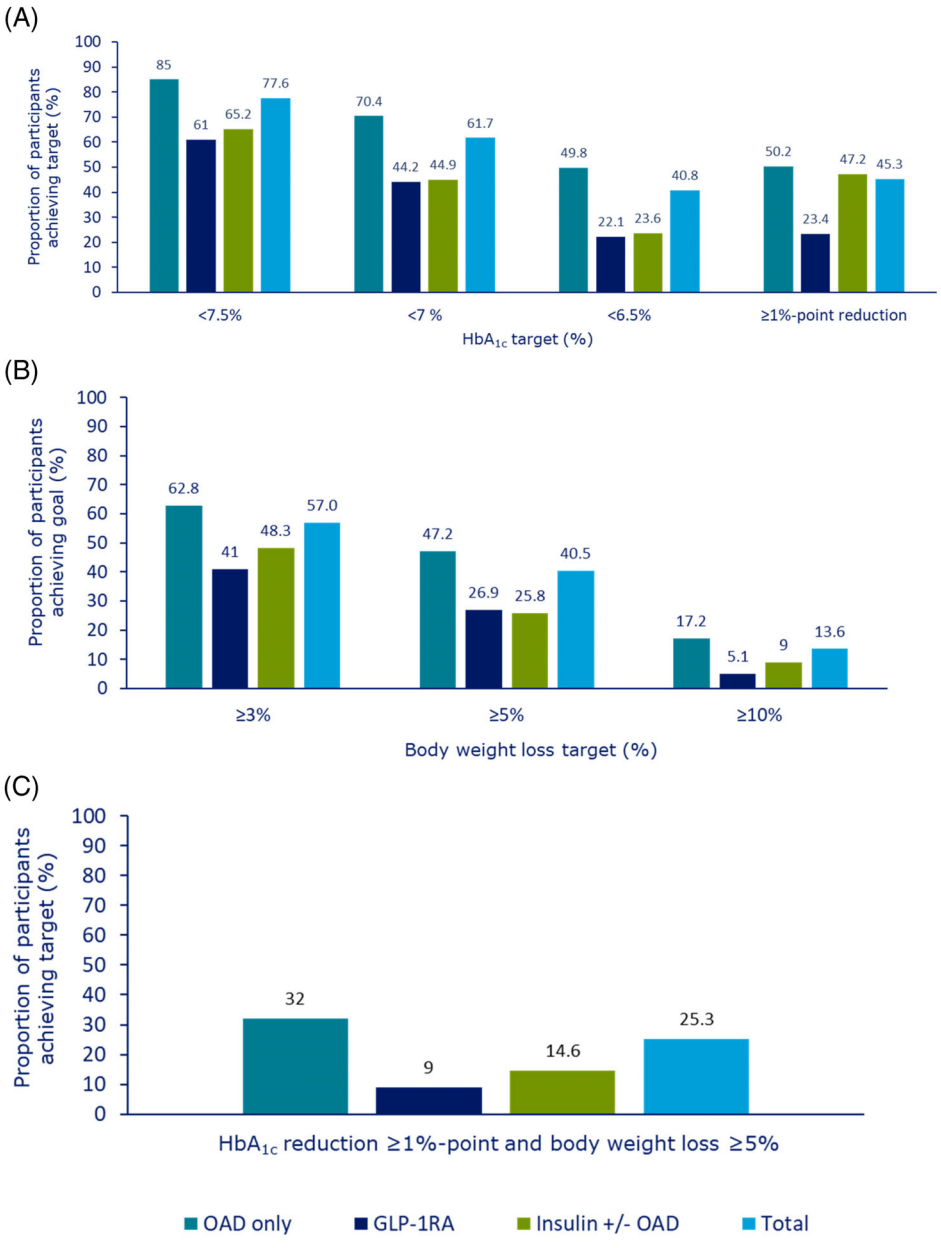

FIGURE 3 Proportion of patients achieving (A) HbA1c targets, (B) weight-loss goals and (C) HbA1c reduction of ≥1.0%-point and body weight loss of ≥5.0% (EAS). Data are based on the EAS, which included patients who attended the EOS visit and were still receiving semaglutide. n = number of patients with available data. EAS, effectiveness analysis set; EOS, end of study; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; OAD, oral antidiabetes drug

TABLE 2 Antidiabetes drug use at baseline and EOS (EAS)

Antidiabetes drug	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)

	Total insulin dose (IU), mean (SD)		
	Baseline	EOS	Number stopped bolus insulin
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

Note: EAS included patients who attended the EOS visit and were still receiving semaglutide. Total insulin includes bolus, basal and premixed insulin.
Abbreviations: 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 antidiabetes drug; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SD, standard deviation.

(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 (Table S3). Body weight also decreased significantly by 4.1 to 4.3 kg across all baseline HbA1c subgroups (Table S3).

In the EAS, the overall change in waist circumference from baseline to EOS was −4.6 cm (95% CI −5.24, −3.91; $P < .0001$) (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.

3.4 | Post-hoc analysis of composite endpoint

The proportion of patients who achieved reduction of HbA1c of ≥1.0%-point and body weight loss of ≥5.0% was 25.3% (Figure 3C).

3.5 | 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; $P < .0001$) and 2.4 (95% CI 1.70, 3.12; $P < .0001$), respectively (Figure S2A,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 the Diabetes Treatment Satisfaction Questionnaire status score was 6.8 points (95% CI 6.30, 7.32; $P < .0001$) (Figure S2C).

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

3.6 | Semaglutide dose at end of study

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 (Table S4).

3.7 | Insulin and antidiabetes drug use

The mean (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 Table S1).

3.8 | 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 ($P < .0001$ for all). Systolic and diastolic blood pressure also decreased significantly from baseline to EOS ($P < .0001$ for both) (Table S5).

3.9 | Safety

Overall, 143 AEs were reported in 81 patients in the FAS during the study regardless of semaglutide treatment status (Table S6); 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. Furthermore, 60 AEs in 35 patients (6.0% of the FAS) led to permanent semaglutide discontinuation, i.e. 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 (Table S6) and two patients (0.4%; four events) in the EAS.

4 | 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 HbA1c, 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 HbA1c were observed in all baseline HbA1c subgroups, the extent of which correlated positively with baseline HbA1c 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 because of 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 HbA1c as quickly as possible while minimizing risk to patients.[6,7] The results of the SURE Italy study are consistent with efficacy and safety data from the SUSTAIN RCTs[13–18] and the SURE studies in Canada,[22] Denmark/Sweden,[23] Spain,[24] Switzerland[25] and the UK[26] and pooled analyses of these studies,[27] 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,[28–32] 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 HbA1c and weight versus the maximum doses of OW exenatide and dulaglutide that are available in Italy.[30]

A strength of the SURE Italy study is its inclusion of an 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.[27] Similarly, in SURE Italy, 'GLP-1RA-experienced' patients had significant reductions in HbA1c, 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 REALIZE-DM[33] and SURE Canada.[22] Similar results were observed in previous retrospective, observational RW studies of OW semaglutide in Italy.[28,30] 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 antidiabetes drugs.[12] However, discontinuation of DPP-4i treatment is recommended when adding GLP-1RA, because of overlapping mechanisms of action.[34] 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.[35] 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.[34]

While the addition of semaglutide has been associated with a decrease in insulin dose in previous studies,[17,23,36] 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 because of the absence of structured algorithms for insulin titration/reduction, and higher fasting plasma glucose and HbA1c indicating poor glycaemic control at baseline, particularly for those who entered the study on insulin. Despite this, the level of hypoglycaemia remained low. Furthermore, despite a reduction in the percentage of patients using sulphonylureas over our study, 8.6% remained on them at EOS, probably because of treatment inertia, as seen in SURE Switzerland[25] and the UK[26]; 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 antidiabetes drugs at the time the study was performed; with the release of Nota 100[37] in May 2022, antidiabetes drugs can

now be prescribed by all specialists of the Italian national health system and by general practitioners, depending on the region. In addition, because of 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 because of 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.[38] Patients switching from another GLP-1RA to OW semaglutide also experienced improvements in HbA1c 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.

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CONFLICTS OF INTEREST

A-MC is an employee of Novo Nordisk and owns stock in the company. ED is an employee of Novo Nordisk. TLB is an employee of Novo Nordisk and owns stock in the company. FG 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.

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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