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Once-weekly semaglutide use in glucagon-like peptide-1 receptor agonist naïve patients with type 2 diabetes in North Macedonia: Real-world data from the MIRAGE study

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ABSTRACT

Aims: The MIRAGE study aimed to evaluate the real-world use of once weekly (OW) subcutaneous semaglutide in glucagon-like peptide-1 receptor agonist naïve type 2 diabetes patients in routine clinical practice in North Macedonia.

Methods: MIRAGE was a multicentre, single-arm, retrospective and 30-weeks study, conducted in North Macedonia. Primary [change in glycated haemoglobin (HbA1c)] and secondary endpoints [change in body weight, fasting plasma glucose (FPG), lipid parameters, blood pressure, waist circumference, glycaemic and weight-loss target achievement] were evaluated between baseline and end of study (EOS).

Results: Baseline characteristics of 314 patients enrolled in the study were, mean age: 55.5 years, HbA1c: 9.0 %, diabetes duration: 7.8 years, body weight: 105.2 kg and waist circumference: 114 cm. Patients at EOS experienced statistically significant estimated mean change in HbA1c: −2.2 % points, body weight: −9.0 kg, and FPG: −4.1 mmol/L (all $p < 0.0001$). At EOS, 62.1 % patients achieved HbA1c < 7 %, and 79.3 % had ≥ 1 % HbA1c reduction. A weight reduction of ≥ 3 % and ≥ 5 % was noted in 88.3 % and 73.3 % patients, respectively. No new safety concern has emerged.

Conclusions: Findings from MIRAGE study demonstrated glycaemic and weight-loss benefits of semaglutide, with improvements in other cardiometabolic parameters. The study supports real-world OW subcutaneous semaglutide use in North Macedonia.

1. Introduction

The Global Burden of Disease study 2021 has estimated that 529 million individuals of all ages are affected with diabetes worldwide, 96 % (~508 million) of which have type 2 diabetes (T2D) [1]. Nearly 80 % of people with T2D live in low- and middle-income countries [2]. Ahmeti et al. 2020 in recent retrospective study demonstrated growing prevalence of T2D from 5.66 % (2015) to 7.2 % (2019) in Republic of Macedonia (a upper-middle-income European country) [3]. The recent American Diabetes Association (ADA) Standards of Diabetes Care recommendations emphasize the importance of achieving target glycaemic level (glycated haemoglobin or HbA1c < 7 %) and managing weight in people with diabetes [4]. However, the majority of people living with T2D face challenges in achieving glycaemic target despite a plethora of treatment options [5].

Glucagon like peptide-1 (GLP-1), an incretin hormone, stimulates

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insulin secretion and inhibits glucagon secretion from pancreas, the effects of which are impaired in T2D [6]. Glucagon like peptide-1 receptor agonists (GLP-1 RAs) are a class of drugs that mimics the action of GLP-1 and thus are utilized in the treatment of T2D due to their proven HbA1c-lowering properties. Semaglutide is a GLP-1 RA that shares 94 % homology with human native GLP-1; once weekly (OW) subcutaneous formulation of semaglutide was approved by the US Food and Drug Administration in 2017 and by the European Medicines Agency in 2018 [7,8].

The efficacy of OW subcutaneous semaglutide in achieving better glycaemic control and weight reduction was found to be significantly better than comparators (like sitagliptin, extended-release exenatide, and dulaglutide) in the Semaglutide Unabated Sustainability in Treatment of T2D (SUSTAIN) global clinical trial programme [9–19]. Furthermore, semaglutide treatment led to larger blood pressure (BP) reductions, and improved health-related quality of life and patient's satisfaction over comparators [20–22]. A significantly lower risk (26 %) of primary composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in patients with T2D was observed in the group treated with OW semaglutide, compared to placebo (both on a standard-care regimen) [14]. Pooled and post-hoc analysis of SUSTAIN trials have demonstrated consistent effects of semaglutide along the diabetes care continuum in a wide range of patient subgroups with varying clinical features [23–25].

The results obtained from phase II/ III clinical trials always demand validation in real-world clinical practice. The Semaglutide Real-world Evidence (SURE) programme included 9 observational real-world studies from 10 countries namely Denmark, Sweden, Switzerland, Canada, Spain, United Kingdom, Netherlands, Italy, Germany, and France [26–34]. In line with the results from SUSTAIN programme, the results from SURE studies and their pooled analysis suggest significant benefits, both for glycaemic control and body weight, in patients with T2D and in diverse subgroups stratified by various baseline characteristics (age, HbA1c, body mass index or BMI, duration of T2D), including prior treatment with a GLP-1 RA other than semaglutide (GLP-1 RA-naïve/ switcher) [26–35]. Independent real-world studies from Japan, Italy, Denmark and Spain also supported the results of SUSTAIN/ SURE programme [36–40].

The present study evaluated the effect of OW subcutaneous semaglutide on the glycaemic control and cardiometabolic outcomes among GLP-1 RA naïve T2D adult patients in routine clinical practice within North Macedonia.

2. Materials and methods

2.1. Study design and procedures

MIRAGE (a study in North Macedonia investigating retrospective data of participants with T2D in real-world environment setting) was a multicentre, single-arm, retrospective, non-interventional, approximately 30-week study, conducted at 41 sites in North Macedonia.

All eligible patients, who initiated treatment with OW semaglutide prior to data collection, were considered for study participation. The physicians were responsible for patient identification and eligibility confirmation through the review of medical records. Relevant data related to clinical parameters of eligible patients were extracted from the existing medical records at baseline, observation period and end of follow-up. The baseline (week 0) was defined as the date of first prescription of OW semaglutide (Ozempic®, Novo Nordisk A/S), administered subcutaneously as prescribed by the treating physician. The end of follow-up was defined as 30 weeks after initiation of OW semaglutide treatment with a window of ± 4 weeks. If multiple measures of HbA1c and other endpoint variables were available within the 30 ± 4 weeks, the measure closest to week 30 was considered as end of study (EOS). Current clinical practices, applicable local labels, and standard of care as per physician's discretion were followed for the patient's treatment.

The study was performed in accordance with the Declaration of Helsinki and the Guidelines for Good Pharmacoepidemiology Practices. Being a retrospective study, informed consent forms and study approval were not required as per the opinion of the Ethics Committee within Agency for Medicines and Medical Devices in North Macedonia. MIRAGE is registered with ClinicalTrials.gov, NCT05468632.

2.2. Study population

The study population included 314 GLP-1 RA naïve (males or females aged ≥ 18 years) T2D patients, who initiated OW semaglutide at least 30 ± 4 weeks prior to data collection (July 05, 2022 to July 31, 2022). The inclusion criteria required one HbA1c measurement at baseline (or most recent value ≤ 12 weeks prior to semaglutide initiation) and at least one HbA1c measurement after baseline. Patients with previous participation in the study, prior use of GLP-1 RA therapy within last one year, or with type 1 or gestational diabetes were excluded from the study.

2.3. Endpoints

Primary endpoint was change in HbA1c from baseline to EOS (30 ± 4 weeks). Secondary endpoints were change in body weight, fasting plasma glucose (FPG), systolic BP (SBP), diastolic BP (DBP), waist circumference, and lipid parameters [total, low-density lipoprotein- (LDL) and high-density lipoprotein- (HDL) cholesterol, and triglycerides], from baseline to EOS. Other categorical (Yes/No) secondary endpoints were proportion of patients achieving HbA1c < 7 %, reduction in HbA1c ≥ 1 %, weight loss ≥ 5 % and ≥ 3 %, composite endpoint of HbA1c reduction ≥ 1 % and weight loss ≥ 3 %, and having at least one severe hypoglycaemic episode. Severe hypoglycaemia was considered when assistance from another person was required for active administration of carbohydrate or glucagon, or for other corrective actions according to ADA (American Diabetes Association). Other parameters such as change in BMI, serum creatinine and estimated glomerular filtration rate (eGFR) were also analysed.

Exploratory endpoints were analysis of semaglutide dose (0.25/0.5/1 mg) at baseline and EOS, and mean weekly dose at EOS. In addition, change from baseline in other anti-hyperglycaemic medications, gastrointestinal (GI) side effects, and hospitalizations related to T2D post-OW semaglutide initiation were dichotomised into Yes/No. Since this study was based on the secondary use of existing data and involved no prospective data collection; therefore, other safety endpoints including adverse events (AEs), adverse reactions, or drug exposure during pregnancies, were not recorded as part of the study.

2.4. Sample size calculation

The sample size calculation was based on the primary endpoint. It was assumed that a minimum sample size of 97 patients would provide 90 % power to detect a minimum difference of 0.5 %±SD in HbA1c between treatment initiation and 30-weeks follow-up [41]. However, with the ultimate aim to provide large data for decision makers, all available data of 350 patients initiated with OW semaglutide, was planned to be collected.

2.5. Statistical analysis

Two-sided statistical tests for the primary (change in HbA1c) and secondary (change in FPG and body weight) endpoints were performed with a 0.05 level of significance. The continuous secondary endpoints such as change in SBP and DBP, waist circumference and lipid parameters were reported using descriptive statistics (Mean ± SD). For dichotomous secondary endpoints, binary categorization was used to calculate the proportion (%) of patients achieving the criteria, HbA1c < 7 %, reduction in HbA1c ≥ 1 %, weight loss ≥ 5 % and ≥ 3 %, HbA1c reduction ≥ 1 % and weight loss of ≥ 3 % from baseline to EOS, and

having at least one severe hypoglycaemic episode at EOS. The analysis of continuous exploratory endpoints were reported using descriptive statistics, and of categorical exploratory endpoints was done by calculating the frequencies i.e., n (%).

The primary analysis of primary and secondary outcomes was performed using full analysis set (FAS). All eligible patients who were notified by the healthcare professional about the usage of their data in the study and initiated treatment with OW semaglutide, were included in FAS. In-study and on-treatment observation periods were defined for FAS. The in-study observation period is the time duration during which patients are considered to be in the study, regardless of adherence to OW semaglutide treatment. The on-treatment observation period is a part of in-study observation period and refers to the time period in which patients are treated with OW semaglutide. The primary analysis (primary and secondary outcomes) was based on FAS for in-study observation period. Patients with an EOS visit outside the original 30 ± 4 weeks were also included in the primary analysis. The primary analysis used a crude and adjusted mixed model for repeated measurements (MMRM). The crude model consisted of baseline HbA1c and time as covariates, whereas the adjusted model included covariates (baseline HbA1c, age, BMI, T2D duration, and time) and fixed factors [study site, sex, dipeptidyl peptidase-4 inhibitors, insulin and number of oral anti-diabetic drugs (OADs) used]. Fixed factors were believed to have an influence on change in HbA1c. To handle the deviation from linearity in time, the crude and adjusted model included an additional continuous second order polynomial function of time (a squared term of time) as covariate. Study site was also included in the model to account for within-site correlation.

Missing data were not imputed for this study. Secondary analysis of the primary and secondary endpoints was also performed on the FAS on-treatment observation period. Sensitivity analysis was performed for the primary endpoint that was based on FAS in-study observation period for the patients who had EOS visit within the original visit window (week 26–34). This was performed to investigate the robustness of the estimate (primary endpoint) from primary analysis.

3. Results

3.1. Patient population and baseline characteristics

A total of 350 patients were planned to be included in this study. However, three sites declined to participate, and five potentially eligible patients from participating sites did not fulfil all the inclusion criteria. Therefore, data from a total of 314 patients from 41 sites were included and constituted FAS. Primary and sensitivity analysis were conducted on 314 and 238 patients, respectively. Of the total 314 patients, 1 patient (0.3 %) discontinued OW semaglutide treatment at the EOS visit. However, the data of this patient was included in the analysis.

At baseline in the FAS, there were a similar proportion of male and female patients with mean age of 55.5 years and age range of 21–82 years. From 260 patients with recorded data on BMI, only 0.4 % patients had normal BMI, while others were overweight or obese (86.5 % had BMI $\geq$ 30 kg/m^2). The most common comorbidities were hypertension and dyslipidaemia, affecting 64.3 % and 56.1 % patients, respectively. A majority of patients initiated a dose of 0.25 mg semaglutide (99.4 %), while 0.6 % received 0.5 mg. At the time of initiating semaglutide, 90.4 % patients were taking other anti-hyperglycaemic medications; metformin (80.9 %) was the most common. Insulins and analogues for injection (fast-acting/ intermediate-acting/ intermediate- or long-acting combined with fast-acting/ long-acting) and sulfonylureas were used in 44.6 % and 10.8 % patients, respectively. Use of dipeptidyl peptidase-4 inhibitor and sodium-glucose co-transporter 2 inhibitors was less common as only 1.6 % and 0.6 % patients respectively were having these anti-hyperglycaemic medications prior to treatment with OW semaglutide (Supplementary Table 1). The mean T2D duration was 7.8 years and mean baseline HbA1c was 9.0 %. Baseline demographic and clinical characteristics are summarized in Table 1.

3.2. Glycaemic control

In the FAS, 233 of 314 patients had complete covariate information and were included in the primary analysis using adjusted MMRM model, based on in-study observation periods. The observed mean HbA1c value at baseline and EOS was 8.9 % and 6.7 %, respectively, resulting in a statistically significant estimated mean change in HbA1c of −2.2 ± 0.06 % points [95 % confidence interval (CI) −2.32; −2.08; p < 0.0001)] as depicted in Fig. 1A. The results from the secondary analysis were consistent with the results of the primary analysis as only one patient reported discontinuation at EOS visit.

Among the 238 patients that had their EOS visit in the original visit window i.e., 26–34 weeks, 172 patients had complete covariate information and contributed to sensitivity analysis of primary endpoint for in-study observation period. An estimated change of −2.0 ± 0.07 % (95 % CI −2.14; −1.87; p < 0.0001) from baseline to EOS (visit within 26–34 weeks) was observed and supported the conclusions obtained from the primary analysis. The estimated HbA1c mean plot (Fig. 1B) is showing decrease in mean HbA1c over time from semaglutide initiation

Table 1
Demographic and clinical characteristics of study patients at baseline.

Characteristic	N	Values
Age, years	314	55.5 ± 10.65
Sex	314	
Female		159 (50.6)
Male		155 (49.4)
Height, cm	260	170.1 ± 8.83
Weight, kg	266	105.2 ± 20.48
BMI, kg/m^2	260	36.26 ± 6.05
Normal, 18.5 to < 25		1 (0.4)
Overweight, 25 to < 30		34 (13.1)
Obese, ≥30		225 (86.5)
Blood pressure, mmHg	213	
Systolic		135.6 ± 13.73
Diastolic		86.4 ± 8.81
Waist circumference, cm	105	114.0 ± 13.70
Duration of T2D, years	280	7.8 ± 6.18
Microvascular complications	314	
Diabetic retinopathy		11 (3.5)
Diabetic neuropathy		21 (6.7)
Diabetic nephropathy		9 (2.9)
Macrovascular complications	314	
Coronary vascular disease		37 (11.8)
Acute myocardial infarction		18 (5.7)
Coronary-artery bypass grafting		7 (2.2)
Percutaneous transluminal coronary angioplasty		24 (7.6)
Cerebrovascular disease		9 (2.9)
Transient ischemic attack		3 (1.0)
Stroke		6 (1.9)
Lower extremity artery disease		6 (1.9)
Hypertension	314	202 (64.3)
Dyslipidaemia	314	176 (56.1)
Hyperuricaemia	314	1 (0.3)
COVID-19	314	12 (3.8)
HbA1c, %	314	9.0 ± 1.78
HbA1c < 7 %	314	32 (10.2)
HbA1c 7 to < 8 %	314	68 (21.7)
HbA1c 8 to < 9 %	314	85 (27.1)
HbA1c ≥ 9 %	314	129 (41.1)
Fasting plasma glucose, mmol/L	272	11.0 ± 3.46
Other antihyperglycaemic medication	314	284 (90.4)
Previously taking medication for COVID-19	314	5 (1.6)
HDL cholesterol, mmol/L	121	1.2 ± 0.46
LDL cholesterol, mmol/L	129	3.0 ± 1.07
Total cholesterol, mmol/L	211	5.0 ± 1.69
Triglycerides, mmol/L	215	2.5 ± 1.62
Serum creatinine, μmol/L	197	79.2 ± 19.19
Dose of semaglutide, mg	314	
0.25		312 (99.4)
0.5		2 (0.6)

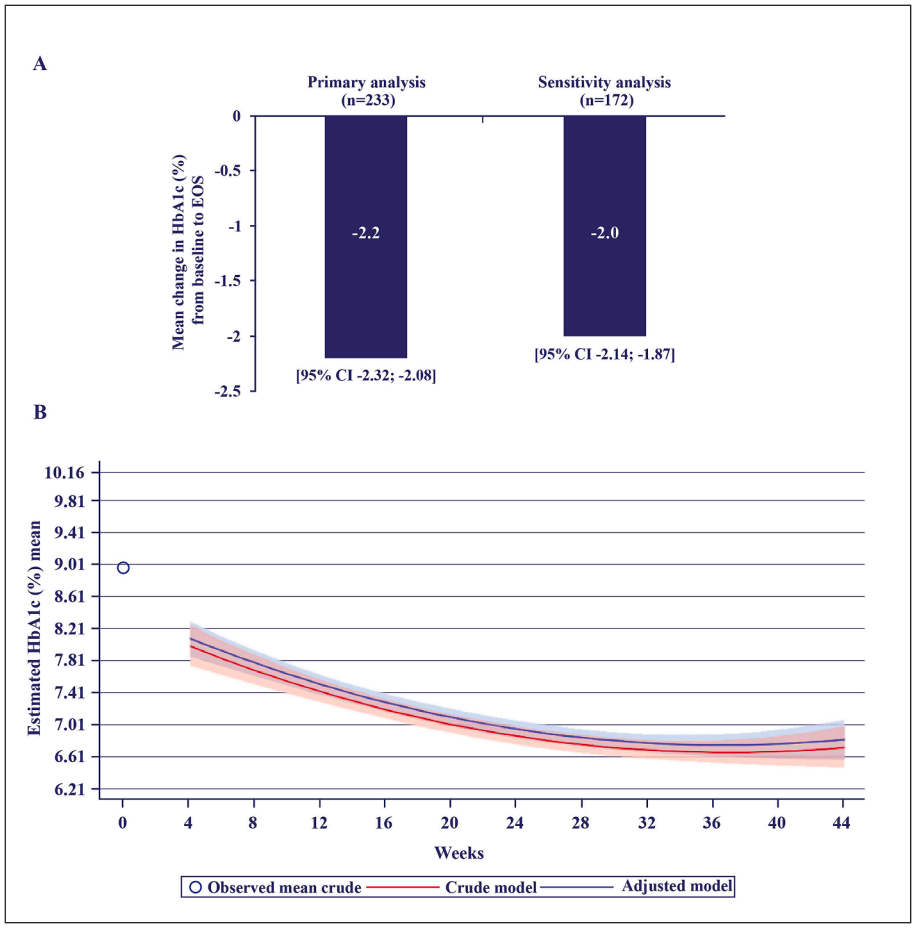

Fig. 1. A. Mean change in HbA1c (%) from baseline to EOS in adjusted MMRM based on in-study observation period. B. Estimated mean HbA1c from primary analysis over time for in-study observation period, FAS. To handle (quadratic) deviation from linearity a random coefficient model with time and time squared as fixed coefficients, patient as random coefficients was used. Adjusted mixed model includes baseline HbA1c, T2D duration, age, BMI, time, time-squared as covariate and sex, site ID, pre-initiation use of DPP-4i (Yes/No), pre-initiation use of insulin (Yes/No), number of oral antihyperglycaemic drugs use pre-initiation as fixed factors with random intercept and random coefficient for time (slope) for each patient. Outer lines of the band represent 95% confidence interval. BMI: Body mass index; DPP-4i: Dipeptidyl peptidase-4 inhibitor; EOS: End of study; FAS: Full analysis set; MMRM: Mixed model for repeated measurements; N: Number contributing to analysis; HbA1c: Glycated haemoglobin; T2D: Type 2 diabetes.

to EOS. The crude MMRM model for change in HbA1c from baseline to EOS provided similar results as the adjusted model.

3.3. Reduction in mean body weight and FPG

Primary analysis for body weight was conducted for 219 patients based on in-study observation period using adjusted MMRM model. The observed mean body weight at baseline and EOS was 105.6 and 96.6 kg, respectively. A statistically significant estimated mean body weight reduction of 9.0 ± 0.59 kg (95 % CI −10.16; −7.81; $p < 0.0001$), corresponding to a relative body weight reduction of 8.3 %±0.57 (95 % CI −9.43; −7.19; $p < 0.0001$) was observed from semaglutide initiation to EOS (Fig. 2A). A total of 200 patients had complete covariate information for adjusted MMRM FPG analysis. From baseline to EOS, a statistically significant mean change of −4.1 ± 0.1 mmol/L (95 % CI −4.29; −3.90; $p < 0.0001$) was observed in FPG (Fig. 2A).

The crude MMRM model for mean change in body weight and FPG produced similar results as the adjusted model from baseline to EOS. The results from the secondary analysis were also consistent with the results of the primary analysis of secondary endpoints.

3.4. Other secondary endpoints

The mean change in waist circumference from baseline (114.0 cm) to EOS (107.7 cm) was –6.3 cm. The mean SBP and DBP were 126.7 and 81.6 mmHg, respectively at EOS with a mean change of −8.9 and −4.8 mmHg from baseline, respectively (Fig. 2B). Similarly, by EOS mean values of total and LDL cholesterol, and triglycerides reduced to 4.5 ± 1.18, 2.5 ± 1.03, and 1.8 ± 0.82 mmol/L, respectively from baseline mean values (5.0 ± 1.69, 3.0 ± 1.07, and 2.5 ± 1.62 mmol/L, respectively). However, HDL cholesterol increased from 1.2 ± 0.46 mmol/L, at baseline to 1.3 ± 0.71 mmol/L, at EOS (Fig. 2C).

At EOS, 62.1 % patients achieved target HbA1c of < 7 %, while 79.3 % patients had ≥ 1 % reduction in HbA1c (Fig. 3). Similarly, 88.3 % and 73.3 % patients had a body weight reduction of ≥ 3 % and ≥ 5 %, respectively. Number of patients achieving body weight reduction of ≥ 10 % is presented in Supplementary Table S2. Moreover, 72.1 % patients achieved HbA1c reduction of ≥ 1 % and body weight reduction of ≥ 3 % from baseline to EOS. Three (1.0 %) patients reported severe hypoglycaemia during the study. All of them were using insulin (basal or premix) in addition to OW semaglutide.

Other parameters like BMI and serum creatinine also reduced from 36.3 kg/m^2 and 79.2 µmol/L at baseline to 33.3 kg/m^2 and 78.9 µmol/L at EOS, respectively (Fig. 2B and C). Mean eGFR was 85.7 ± 18.29 mL/min/1.73 m^2 at baseline and 85.0 ± 19.41 mL/min/1.73 m^2 at EOS. Proportion of patients with eGFR < 60 mL/min/1.73 m^2 at baseline and EOS was 10,2% and 12,7%, respectively. (Supplementary Table 3).

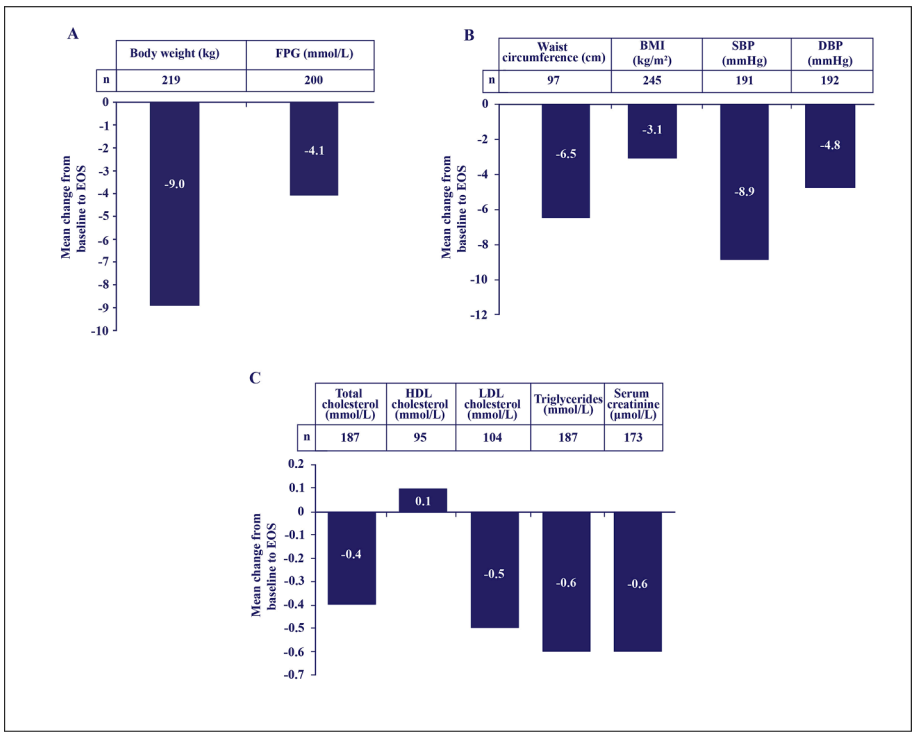

Fig. 2. Mean change from baseline to EOS in A. Body weight and FPG in adjusted MMRM based on in-study observation period, B. Waist circumference, BMI, SBP and DBP, and C. Total, HDL and LDL cholesterol, triglycerides and serum creatinine BMI: Body mass index; DBP: Diastolic blood pressure; EOS: End of study; HbA1c: Glycated haemoglobin; HDL: High density lipoprotein; LDL: Low density lipoprotein; FPG: Fasting plasma glucose; SBP: Systolic blood pressure.

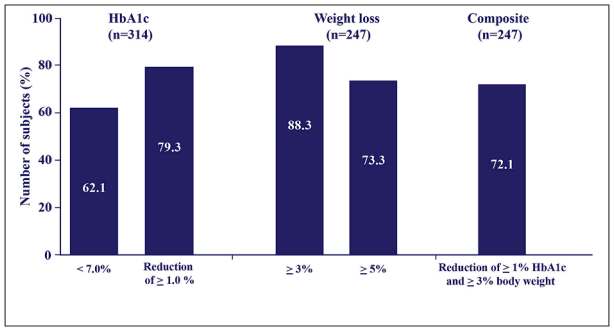

Fig. 3. Proportion of patients achieving HbA1c targets, weight-loss goals and composite endpoint of HbA1c reduction of ≥ 1 % and weight loss of ≥ 3 %. HbA1c: Glycated haemoglobin.

3.5. Exploratory endpoints

At EOS, majority of patients (89.2 %) were on 1 mg dose, followed by 10.5 % and 0.3 % patients, who were on 0.5 and 0.25 mg dose of semaglutide, with mean ± SD dose of 0.95 ± 0.16 mg. A total of 46 (14.6 %) patients had GI side effects and 3 (1.0 %) patients had T2D-related hospitalization during the study.

The mean number of anti-hyperglycaemic medications used by patients increased from the time of OW semaglutide initiation (1.4 medications) to EOS (2.5 medications). It should be noted that this increase was because of the inclusion of OW semaglutide in EOS assessment, while not at baseline.

4. Discussion

The MIRAGE is the first study to investigate the outcomes associated with OW semaglutide (0.25–1 mg) treatment in GLP-1 RA naïve adults with T2D in a real-world clinical setting within North Macedonia. The study findings demonstrated that OW subcutaneous semaglutide resulted in statistically significant reduction ($p < 0.0001$) of −2.2 % points in HbA1c from baseline to EOS. With a mean baseline HbA1c of 9.0 %, almost two third of patients reached treatment targets of HbA1c < 7 % by week 30 of semaglutide therapy. The results complemented the findings of SUSTAIN and SURE study programmes. The results of SUSTAIN programme demonstrated that 0.5–1.0 mg OW semaglutide given for 30–56 weeks reduced HbA1c by 1.5–1.8 % with HbA1c < 7 % achieved in 67–79 % patients [42]. The studies of SURE programme also showed a reduction in HbA1c from baseline to EOS in the range of 0.8–1.5 % points [26–34]. In Italian individuals with established diagnosis of T2D, OW semaglutide treatment for 6 and 12 months demonstrated reduction of HbA1c by −1.02 % and −1.1 %, respectively [37]. Moreover, other independent real-world studies have supported the use of OW semaglutide in routine clinical practice due to pronounced improvements in glycaemic control [36,38–40]. A meta-analysis of 26 studies found OW semaglutide (1.0 mg) add-on therapy to OADs for 6 months as the most effective GLP-1 RA amongst comparators (liraglutide, dulaglutide, exenatide, lixisenatide, and albiglutide), in terms of glycaemic control and weight loss [43].

At EOS, the patients in MIRAGE study have experienced statistically significant decrease in FPG level (−4.1 mmol/L) from baseline. A significant reduction in FPG by OW semaglutide has also been observed in independent real-world studies [37,38]. A previous randomized clinical trial observed a change in mean FPG level of −3.1 mmol/L from baseline to week 26, with OW semaglutide vs. placebo,in patients with T2D [44]. A meta-analysis of 9 trials also reported significant decrease in FPG (weighted mean difference of −1.15 mmol/L; 95 % CI, −1.67 to −0.63, $p < 0.001$) in addition to HbA1c with OW semaglutide in people with T2D [45].

The majority of the patients in MIRAGE study were obese (86.5 % had BMI ≥ 30 kg/m^2), which was reflected in the mean baseline body weight (105.2 kg), BMI (36.26 kg/m^2) and waist circumference (114.0 cm). From baseline, 73.3 % participants reached clinically relevant body weight loss (≥5%), with an overall mean weight reduction of 9.0 kg; the

weight loss was higher than the findings of the 10-country SURE programme studies [26–34]. Body weight reductions in SUSTAIN and SURE studies were ranged from −3.6 to −6.5 kg and −4.2 to −7.8 kg, respectively [26–34,46]. A cohort study noted weight reduction of ≥ 5 % in 21.2 % and 25.4 % Italian patients with diabetes after 6 and 12 months of OW semaglutide treatment, respectively [37]. A retrospective study from Spain observed body weight reductions of −12.4 kg in GLP-1 RA-naïve patients, with 76.4 % achieving > 5 % weight loss [38]. The weight loss plays a crucial role in lowering cardiovascular risk by decreasing triglycerides, total cholesterol and LDL cholesterol that is linked with > 5 % weight loss [47]. The present study also demonstrated substantial improvements in cardiovascular risk profile, indicated by findings of SBP and DBP, total cholesterol, LDL cholesterol, and triglycerides at EOS. The study results were consistent with the profile of OW semaglutide from SUSTAIN 6 trial and a naïve cohort study [14,40].

The function of GLP-1 RAs is glucose-dependent, hence risk of hypoglycaemia is low, and it yields favourable HbA1c and body weight outcomes [48]. SUSTAIN 6 trial shown to have comparable occurrence of severe hypoglycaemia with semaglutide and placebo, along with frequent GI disorders of mild-to-moderate nature during the first 30 weeks of treatment [14]. In the current study, only 1 % patients experienced severe hypoglycaemic episodes, 1 % were hospitalized, and 14.6 % had GI side effects. Apart from these, there were no new safety concerns, indicating favourable risk–benefit balance of OW semaglutide. Existing meta-analyses reported that OW semaglutide is well-tolerated and not linked with a rise in discontinuations due to AEs, compared to other GLP-1 RAs [43,49,50]. Only 1 out of 314 patients of the present study reported treatment discontinuation, depicting adherence to OW semaglutide treatment. In this study, by EOS, the dose was escalated to the maximum semaglutide dose. OW semaglutide dose of 0.25 mg was administered in majority of the patients (99.4 %) at baseline while most patients (89.2 %) were on 1 mg dose of OW semaglutide at EOS, resulting in a mean dose of 0.95 mg at EOS.

Following are the points of potential strength of the study. Being non-interventional and retrospective in design, this study involved no intervention, did not impact usual medical care or affect the treatment of the patients. The study reflected real-world medical practice without the potential for physician response bias, which generally occurs in prospective studies. Furthermore, the selected 41 sites covered all main geographical regions in North Macedonia. Other advantages were the broad eligibility criteria and excellent rates of adherence to the treatment regimen. Nevertheless limitations of the study included lack of thorough mandatory assessments at predetermined time points, as in prospective studies, which may have compromised the robustness and completeness of findings due to potential confounding factors like lifestyle changes. As the data was extracted from existing patients' records it cannot be clearly concluded whether the low rate of microvascular complications reported at baseline was due to underreporting, or doctors' selection of patients predominantly with macrovascular complications. Another potential limitation is absence of analysis of change in other anti-diabetic medication drug doses (especially insulin) upon semaglutide administration. Furthermore, this is a single-arm study and lacks a comparator, hence it could not be directly concluded that the estimated changes in outcomes were causal effects of study treatment.

The retrospective non-interventional MIRAGE study confirmed that the use of OW subcutaneous semaglutide in real-world clinical practice in a diverse population of GLP-1 RA naïve T2D patients of North Macedonia is beneficial. Overall, the patients experienced statistically significant reduction in HbA1c, body weight and FPG level, along with improvements in various cardiometabolic parameters, consistent with findings established in SUSTAIN/ SURE programme. There were no new safety concerns that emerged from this study. The MIRAGE study findings provide robust evidence about the real-world use of OW subcutaneous semaglutide and indicate that it presents a valuable therapeutic option for T2D patients in North Macedonia.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Author TM has been invited speaker and/or attended advisory boards and received honorarium or consultant fees from Alkaloid, Belupo Boehringer Ingelheim, Berlin-Chemie, Krka, Merck, Novo Nordisk, Sanofi and TEVA (Pliva). Author BCM is an employee in Novo Nordisk Farma DOOEL, Skopje, North Macedonia and owns stocks in the company Novo Nordisk A/S. Author SJM has been invited speaker and/or attended advisory boards, and received honorarium or consultant fees from Alkaloid, Boehringer Ingelheim, Berlin-Chemie, Bayer, Krka, Lek Skopje (Sandoz), Merck, Novo Nordisk, Sanofi and Roche Diabetes. Author IBM has been invited speaker and/or attended advisory boards, and received honorarium or consultant fees from Boehringer, Belupo, Krka, Merck, and Novo Nordisk. Author IA has been invited speaker and/or attended advisory boards, and received honorarium or consultant fees from Belupo, Boehringer Ingelheim, Merck, MSD, Novo Nordisk, Sanofi, Roche Diagnostics and TEVA (Pliva).].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.111018.

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