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Real-World Evidence of the Effectiveness and Safety of Biosynthetic Semaglutide in Type 2 Diabetes: A Multicentre Study From Pakistan

Arshad Hussain[1] | Muhammad Umar Wahab[2] | Saleem Qureshi[3] | Umar Yousaf Raja[4] | Atif Munir[5] | Shahnawaz Gardezi[6] | Musarrat Iqbal[3] | Bilal Afzal[7] | Muhammad Daoud Butt[8] | Siew Chin Ong[8]

[1]North-West General Hospital, Peshawar, Pakistan | [2]Umar Diabetes and Foot Care Centre and Umar Diabetes Foundation, Islamabad, Pakistan | [3]Department of Medicine, Center for Diabetes and Liver Disease, Islamabad, Pakistan | [4]Shifa International Hospitals Ltd., Islamabad, Pakistan | [5]Omer Hospital, Lahore, Pakistan | [6]City Hospital, Multan, Pakistan | [7]Mukhtar A Sheikh Hospital, Multan, Pakistan | [8]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Pulau Penang, Malaysia

Correspondence: Muhammad Daoud Butt (daoudbutt@usm.my) | Siew Chin Ong (siewchinong@usm.my)

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ABSTRACT

Aims: To evaluate the real-world effectiveness, safety and patient-reported outcomes of biosynthetic semaglutide in adults with type 2 diabetes mellitus (T2DM) receiving routine outpatient care in a cost-constrained setting.

Methods: This 30-week, prospective, multicentre, non-interventional study enrolled adults with T2DM initiating biosynthetic semaglutide. The primary endpoint was change in glycated haemoglobin (HbA1c) from baseline to end of study (EOS). Secondary endpoints included changes in body weight, waist circumference, patient-reported outcomes (DTSQs and SF-36v2) and safety.

Results: Among 217 patients, mean HbA1c decreased from 9.27% to 7.41% at EOS (−1.86%; $p < 0.001$). At EOS, 76.6% achieved HbA1c < 8.0% and 38.7% achieved < 7.0%. Mean body weight decreased by −7.84 kg ($p < 0.001$), with 76.5% achieving ≥ 5% weight loss. Significant reductions were also observed in body mass index and waist circumference. Treatment satisfaction and physical quality of life improved significantly. Adverse events were predominantly non-serious and gastrointestinal. No severe hypoglycaemic episodes occurred.

Conclusions: In routine clinical practice, biosynthetic semaglutide was associated with clinically meaningful improvements in glycaemic control, body weight and physical quality of life. The safety profile remained consistent with established semaglutide therapy.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12625000610437

1 | Introduction

Type 2 diabetes mellitus (T2DM) remains a profound global health crisis, projected to affect 853 million adults by 2050. The burden is disproportionately concentrated in low- and middle-income countries (LMICs), where cardiovascular disease (CVD) remains the primary driver of mortality [1–4]. Hyperglycaemia-related cardiovascular deaths underscore the urgent need for therapies providing benefits beyond glycaemic control [5, 6]. The burden of diabetes is concentrated in low- and middle-income countries, where delayed diagnosis, limited access to care and high out-of-pocket costs contribute

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to poorer outcomes [2, 7, 8]. Globally, an estimated 252 million people remain undiagnosed, nearly 90% residing in LMICs [2, 7, 9].

Pakistan currently faces the highest age-standardised diabetes prevalence globally, affecting approximately 34.5 million people (31.4% of adults). This crisis is compounded by a 27% undiagnosed rate, low healthcare expenditure (< USD 100 per capita) and high out-of-pocket costs, leading to over 225 000 annual deaths [2, 10–12]. While ADA/EASD guidelines recommend glucagon-like peptide-1 receptor agonists (GLP-1RAs) like semaglutide for their superior cardiorenal and weight-loss benefits, innovator semaglutide remains inaccessible for most Pakistani patients due to high acquisition costs [13–15].

The SUSTAIN clinical trial programme and real-world evidence from high-income countries have confirmed semaglutide's robust efficacy, typically achieving HbA1c reductions of 1.2%–1.8% and significant weight loss. However, this 'treatment gap' persists in LMICs [16–19]. In the cardiovascular outcomes trial SUSTAIN 6, semaglutide reduced the risk of major adverse cardiovascular events by 26% compared with placebo in patients with T2DM at high cardiovascular risk [20–22].

Despite this robust efficacy profile, access to innovator semaglutide remains severely constrained in LMICs. In Pakistan and similar settings, high acquisition costs and lack of reimbursement frequently result in short-term or intermittent use, dose under-titration or premature discontinuation driven by affordability rather than clinical response [2, 11, 21]. This divergence between guideline-recommended therapy and real-world feasibility has created a substantial treatment gap.

Real-world evidence (RWE) studies from Europe and North America have shown that the metabolic benefits of innovator semaglutide are largely preserved outside randomised trial settings. Observational studies report mean HbA1c reductions of approximately 0.9–1.2 points over 6–12 months, alongside weight loss of 3–5 kg, across routine care populations with substantial baseline comorbidity burdens [23–25]. Biosynthetic semaglutide has emerged as a scalable, high-fidelity alternative to address these affordability challenges [26, 27]. However, there is a paucity of clinical evidence evaluating its performance in routine clinical care within high-burden LMIC settings. While our study focuses on the direct cardiometabolic and quality-of-life impacts of biosynthetic semaglutide, the future of comprehensive diabetes management increasingly relies on the integration of advanced prognostic biomarkers and patient-centred technologies. For instance, recent real-world evidence highlights the prognostic value of novel composite inflammatory and metabolic indices, such as the glucose-potassium ratio (GPR) [28] and the neutrophil-to-prognostic-nutritional-index ratio [29], which could potentially be utilised alongside GLP-1 RA therapy to further refine cardiovascular risk stratification. Furthermore, unlocking the full pleiotropic potential of GLP-1 RAs may require exploring fundamental molecular pathways involved in tissue repair, such as the LncRNA Bmp1/miR-128-3p/PHF6/PI3K/AKT axis [30].

The objective of this study was therefore to evaluate the real-world clinical effectiveness, safety and patient-reported outcomes of biosynthetic semaglutide in adults with T2DM receiving routine clinical care. The primary objective was to assess the change in HbA1c over approximately 30 weeks of treatment. Secondary objectives included changes in body weight, cardiometabolic parameters, treatment persistence, adverse events and validated measures of treatment satisfaction, medication adherence and health-related quality of life.

2 | Methods

2.1 | Study Design

This was a prospective, multicentre, non-interventional, observational real-world study conducted over a period of approximately 30 weeks to evaluate the clinical effectiveness, safety and patient-reported outcomes associated with biosynthetic semaglutide in adults with T2DM receiving routine outpatient care in Pakistan. The study was designed to reflect real-world clinical practice and did not involve any protocol-mandated treatment decisions, diagnostic procedures or follow-up interventions beyond those routinely performed as part of standard care [31].

The decision to initiate biosynthetic semaglutide, continue therapy, adjust dosage or discontinue treatment was made solely at the discretion of the treating physician and was entirely independent of the decision to enrol patients into the study. Biosynthetic semaglutide was administered once weekly via subcutaneous injection using commercially available prefilled pen devices, in accordance with routine clinical practice. Available doses included 0.25, 0.5 and 1.0 mg once weekly, with dose escalation, maintenance or dose reduction determined by individual clinical response and tolerability. Concomitant lifestyle interventions and use of other antihyperglycemic therapies were permitted throughout the study.

Following provision of written informed consent, patients were enrolled at the initiation visit (baseline, Week 0), at which time biosynthetic semaglutide therapy was initiated or confirmed if recently started. Patients were subsequently followed during routine clinical visits according to local practice patterns, with an interim assessment between Weeks 12 and 18 and a predefined end-of-study visit at Week 30. No additional study-specific visits, investigations or procedures were required.

The study was conducted across multiple outpatient diabetes clinics within both public and private healthcare facilities in Pakistan, including tertiary care public hospitals, private hospitals, specialist diabetes centres and community-based endocrinology practices. Study sites were geographically distributed across major administrative regions, including Punjab, Sindh, Khyber Pakhtunkhwa, Balochistan, the Islamabad Capital Territory and Azad Jammu and Kashmir. Participating centres were located in both provincial capitals and secondary cities and served predominantly urban and semi-urban populations. The geographic distribution of participating sites and patient recruitment is shown in Figure S1.

The study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Pharmacoepidemiology Practices. Ethical approval was obtained from the Human

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Research Ethics Committee and relevant local institutional review boards. All participants provided written informed consent before any study-related data collection.

2.2 | Study Population

Male and female adults aged 18 years or older with a confirmed diagnosis of T2DM for at least 12 weeks before enrolment were eligible for inclusion. Patients were required to have a documented HbA1c measurement obtained within 12 weeks before initiation of biosynthetic semaglutide and to be receiving biosynthetic semaglutide as part of routine diabetes management.

Patients were excluded if they had participated in another clinical trial within the preceding 90 days, had known hypersensitivity to semaglutide or its excipients, were pregnant or lactating, or had any condition that, in the opinion of the treating physician, would interfere with safe participation or reliable data collection. Patients with significant cognitive impairment or language barriers that precluded informed consent were also excluded.

2.3 | Study Endpoints

2.3.1 | Primary Endpoint

The primary endpoint of the study was the change in glycated haemoglobin (HbA1c) from baseline to the end-of-study visit, expressed both as absolute percentage-point change and as mmol/mol.

2.3.2 | Secondary Endpoints

Secondary endpoints included changes from baseline to end of study in body weight and waist circumference, proportions of patients achieving HbA1c targets below 8.0%, 7.5% and 7.0%, and the proportion achieving a reduction in HbA1c of at least one percentage point. Additional secondary outcomes included the proportions of patients achieving body-weight reductions of at least 3% and 5%, the proportion achieving a composite endpoint of HbA1c reduction of at least one percentage point combined with at least 3% weight loss, and treatment retention, defined as the proportion of patients remaining on biosynthetic semaglutide at the end of the study (EOS).

2.3.3 | Patient-Reported Outcomes

Treatment satisfaction was evaluated using the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) at baseline and end-of-study visits. Health-related quality of life was assessed using the Short Form-36 Health Survey version 2 (SF-36v2), with changes in the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores evaluated from baseline to end of study. Additional patient-reported measures collected during the study are reported separately.

2.3.4 | Exploratory Endpoints

Exploratory assessments included the weekly dose of biosynthetic semaglutide at the EOS, the median time to achieve the maximum maintenance dose, the proportion of patients who did not require intensification with additional antihyperglycaemic medications during follow-up, and physician-assessed clinical success in relation to the indication for initiating semaglutide therapy. The incidence of documented and severe hypoglycaemic episodes was also recorded. Furthermore, the incidence of specific adverse drug reactions, particularly gastrointestinal events leading to treatment discontinuation, was evaluated and stratified by the maximum tolerated dose. Changes in systolic and diastolic blood pressure and changes in lipid parameters, including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides, were evaluated as post hoc exploratory outcomes.

2.3.5 | Safety Assessments

Safety was assessed throughout the study observation period. All adverse events occurring between the time of informed consent and the EOS visit were recorded by treating physicians during routine clinical encounters. Patient-reported documented hypoglycaemic episodes were recorded, and severe hypoglycaemia was defined as any episode requiring assistance from another person to administer carbohydrate, glucagon or other corrective measures. Adverse events leading to treatment discontinuation were documented and summarised descriptively.

2.3.6 | Statistical Analysis

Descriptive statistics were used to summarise patient demographic and clinical characteristics at the time of initiation of biosynthetic semaglutide. Continuous variables were described using mean ± standard deviation (SD) and median with range, while categorical variables were summarised using frequencies and proportions.

The full analysis set (FAS) included all patients who provided written informed consent and initiated treatment with biosynthetic semaglutide. The effectiveness analysis set (EAS) consisted of all patients who completed the study and were receiving biosynthetic semaglutide at the EOS visit, as assessed by the treating physician. Effectiveness analysis of the primary and secondary endpoints was conducted using the EAS.

The primary analysis of the primary endpoint (change in HbA1c from baseline to EOS) and key secondary endpoints was performed using an analysis of covariance (ANCOVA) model, with change from baseline included as the dependent variable. Prior to interpreting the ANCOVA results, foundational model assumptions were formally verified. The normality of model residuals was confirmed using visual inspection of Q–Q plots alongside the Kolmogorov–Smirnov test. Furthermore, the assumption of homogeneity of variances across groups was validated using Levene's test, confirming the suitability of parametric modelling for these continuous outcomes. The model was adjusted for the baseline value of the respective outcome variable. Patients with

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missing outcome data at the EOS visit were excluded from the primary analysis.

Results are presented as the number of patients with available data, adjusted mean changes from baseline, and associated two-sided 95% confidence intervals (CIs) and *p*-values, as appropriate.

To rigorously address potential attrition and per-protocol bias, two additional analytical frameworks were employed. First, baseline characteristics between study completers (EAS) and non-completers (dropouts/lost to follow-up) were compared using independent samples *t*-tests and Chi-square contingency tests to rule out systematic selection bias. Second, a formal intention-to-treat (ITT) analysis was performed on the entire FAS ($N = 268$) utilising the last observation carried forward (LOCF) imputation method to conservatively estimate treatment effectiveness inclusive of patients with missing EOS outcome data.

Furthermore, to address potential confounding and isolate the independent effect of baseline covariates on treatment response, a multiple linear regression (MLR) model was constructed. The model predicted the absolute change in HbA1c at 6 months while simultaneously adjusting for age, sex, duration of T2DM, baseline BMI, baseline HbA1c, physical activity level, baseline insulin use and the total burden of concomitant oral antidiabetic drugs (OADs).

Safety analyses were conducted descriptively for all patients in the FAS and included all adverse events reported between the time of informed consent and the EOS visit. All statistical tests were two-sided, and a *p*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using Python (version 3.10) and R software (version 4.3.1).

3 | Results

Patient disposition is shown in Figure S2. Of 437 patients screened, 309 provided written informed consent, of whom 41 declined further participation and 12 did not initiate biosynthetic semaglutide. A total of 268 patients completed the baseline assessment and were included in the FAS.

Of the 268 patients in the FAS, 221 patients completed the study, 34 patients discontinued study treatment and 13 patients had an unknown treatment status at the EOS. Of those who completed the study, 217 patients were receiving biosynthetic semaglutide at EOS and therefore comprised the EAS as presented in Figure 2.

3.1 | Assessment of Attrition Bias

To address the potential for selection or attrition bias due to study dropout ($N = 51$), a comparative baseline analysis was conducted between study completers and non-completers. There were no statistically significant differences between the two cohorts concerning age ($p = 0.411$), gender distribution ($p = 0.271$), duration of T2DM ($p = 0.824$), baseline HbA1c ($p = 0.362$) or baseline BMI ($p = 0.825$) as presented in Table S1. The comparability of these baseline parameters indicates that attrition was likely random rather than driven by baseline disease severity or demographic factors, thereby preserving the generalisability of the effectiveness outcomes observed in the completing cohort.

3.2 | Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics of patients included in the FAS are summarised in Table 1. The study population had a mean age of 47.2 ± 11.9 years, with a slight predominance of male participants (53.0%). The mean duration of T2DM was 9.5 ± 6.9 years, indicating a predominantly long-standing disease population.

At baseline, patients exhibited poor glycaemic control, with a mean HbA1c of $9.2\% \pm 1.5\%$. Obesity was highly prevalent, with a mean body weight of 91.1 ± 15.7 kg and a mean body mass index of $33.6 \pm 6.4\ kg/m^2$.

Comorbid conditions were common. Hypertension was present in 56.6% of patients, dyslipidaemia in 50.6% and established CVD in 22.4%. Baseline blood pressure values reflected an elevated cardiometabolic risk profile, with a mean systolic blood pressure of 135.4 ± 14.5 mmHg and a mean diastolic blood pressure of 84.5 ± 8.9 mmHg.

Patients presented with a heavily pre-treated baseline antihyperglycemic profile, characterised by high utilisation of foundational oral agents, such as SGLT-2 inhibitors and Metformin, as well as a significant reliance on exogenous basal and premixed insulin regimens. A complete, granular breakdown of all concomitant background medications at baseline, alongside their subsequent de-escalation at 6 months, is detailed in Table S2.

3.3 | Glycaemic Control (HbA1c)

Overall, patients experienced a clinically meaningful reduction in HbA1c during treatment with biosynthetic semaglutide. In the EAS, mean HbA1c decreased from 9.27% (SD 1.50) at baseline to 7.41% (SD 0.83) at the end of study (EOS), corresponding to an absolute mean reduction of −1.86% points from baseline ($p < 0.001$; Table 2).

The magnitude of HbA1c reduction exceeded thresholds commonly regarded as clinically meaningful in real-world diabetes care. At EOS, a substantial proportion of patients achieved guideline-relevant glycaemic targets. Overall, 84.2% of patients achieved HbA1c < 8.0%, 71.4% achieved HbA1c < 7.5% and 38.7% achieved HbA1c < 7.0% (Figure 1). Furthermore, most patients achieved an HbA1c reduction of ≥ 1.0% from baseline, indicating a robust glycaemic response at the individual patient level.

Changes in HbA1c over time are summarised in Figure 1. Figure 1A illustrates the distribution of HbA1c values at baseline, 3 months, and 6 months, demonstrating a clear leftward shift of the distribution over time. Figure 1B shows the mean HbA1c trajectory with 95% confidence intervals, confirming

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TABLE 1 | Baseline demographic and clinical characteristics of the study population.

Characteristic	Value
Age (years)	47.2 ± 11.9 (median: 48.0, IQR: 39.8–55.0)
Gender	
Male	142 (53.0%)
Female	126 (47.0%)
Smoking status	
Non-smoker	214 (79.9%)
Smoker	54 (20.1%)
Physical activity level	
Sedentary	104 (38.8%)
Lightly active	97 (36.2%)
Moderately active	54 (20.1%)
Very active	13 (4.9%)
Duration of T2DM (years)	9.5 ± 6.9 (median: 8.7, IQR: 3.5–13.6)
Family history of diabetes	
No	120 (44.9%)
Yes	147 (55.1%)
Comorbidities	
Cardiovascular disease (CVD)	60 (22.4%)
Hypertension	151 (56.6%)
Dyslipidaemia	135 (50.6%)
Other comorbidities	71 (26.6%)
Baseline clinical parameters	
Weight (kg)	91.1 ± 15.7 (median: 91.1, IQR: 81.0–100.0)
BMI (kg/m^2)	33.6 ± 6.4 (median: 33.0, IQR: 29.3–37.6)
HbA1c (%)	9.2 ± 1.5 (median: 8.9, IQR: 8.2–10.0)
Fasting plasma glucose (mg/dL)	152.1 ± 32.5 (median: 152.0, IQR: 128.5–175.7)
Systolic BP (mmHg)	135.4 ± 14.5 (median: 136.0, IQR: 123.0–149.0)
Diastolic BP (mmHg)	84.5 ± 8.9 (median: 85.0, IQR: 76.8–92.0)

TABLE 2 | Longitudinal change from baseline to end of study (EOS) in HbA1c, body weight and waist circumference in the effectiveness analysis set (EAS).

Endpoint	Patients analysed, *n*	Baseline, mean (SD)	EOS, mean (SD)	Change from baseline, mean	95% CI	*p*
HbA1c (%)	217	9.27 (1.50)	7.41 (0.83)	−1.86	[−1.98 to −1.74]	< 0.001*
Body weight (kg)	217	91.74 (14.01)	83.90 (13.20)	−7.84	[−8.45 to −7.23]	< 0.001*
Waist circumference (cm)	218	103.65 (15.71)	96.93 (14.84)	−6.72	[−7.35 to −6.09]	< 0.001*

Note: Changes from baseline were assessed using an adjusted analysis of covariance (ANCOVA) model.
*$p < 0.05$.

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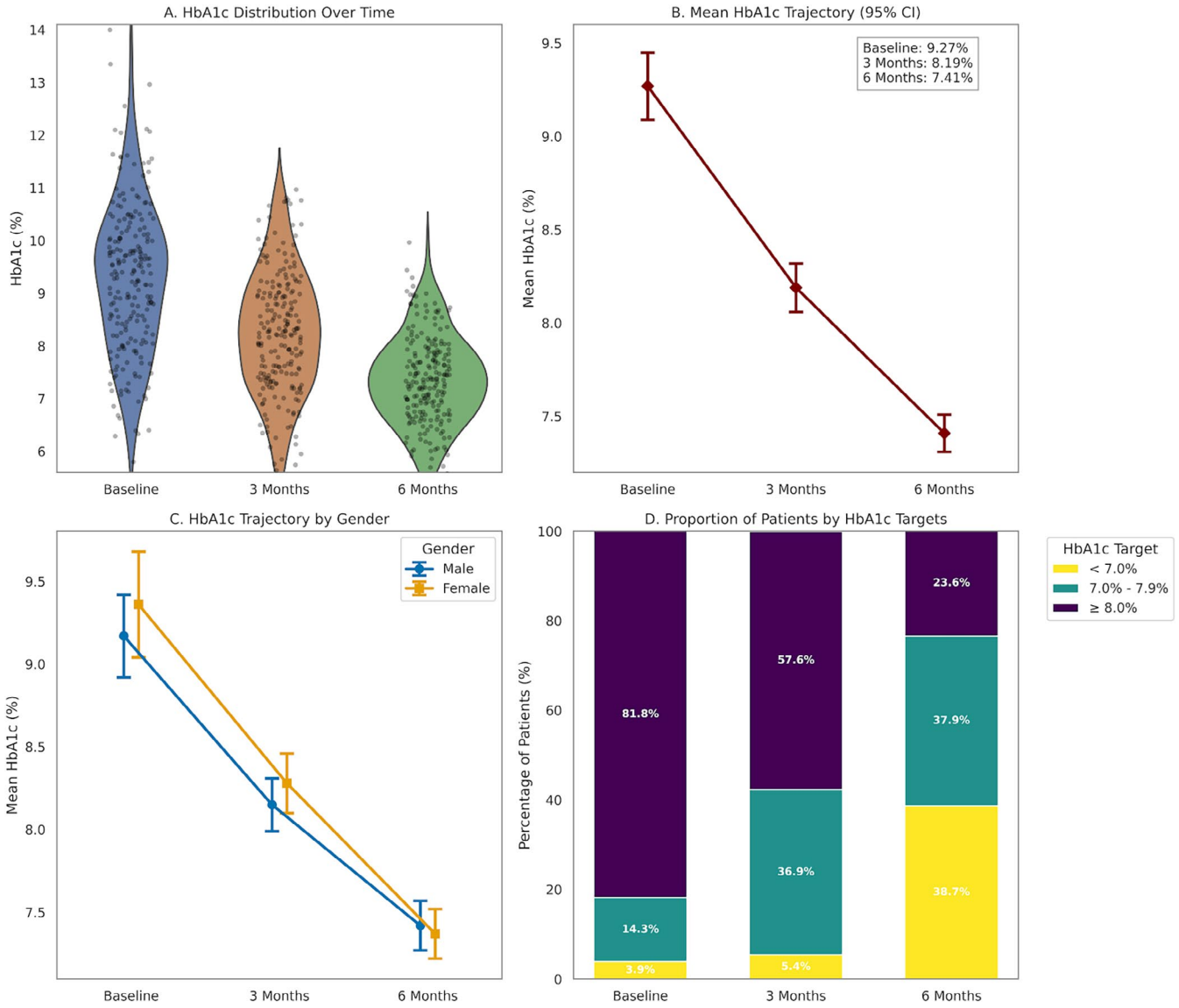


FIGURE 1 | Changes in glycated haemoglobin (HbA1c) over time following initiation of biosynthetic semaglutide. (A) HbA1c distribution over time, (B) mean HbA1c trajectory (95% CI), (C) HbA1c trajectory by gender and (D) proportion of patients by HbA1c targets.

a sustained decline in mean HbA1c throughout follow-up. Figure 1C presents sex-stratified HbA1c trajectories, with parallel reductions observed in both male and female participants, indicating consistent glycaemic responses across sexes. Summary statistics for the change in HbA1c from baseline to EOS, derived from the adjusted ANCOVA model, are presented in Table 2.

3.4 | Body Weight

Overall, patients experienced a clinically meaningful reduction in body weight during treatment with biosynthetic semaglutide. In the EAS, mean body weight decreased from 91.74 kg (SD 14.01) at baseline to 83.90 kg (SD 13.20) at the end of study (EOS), corresponding to an absolute mean reduction of −7.84 kg from baseline ($p < 0.001$; Table 2).

Changes in body weight over time are summarised in Figure 2, which provides complementary distributional, longitudinal and subgroup perspectives. Figure 2A illustrates the distribution of body weight at baseline, 3 months, and 6 months, demonstrating a consistent leftward shift of the distribution over time, indicative of weight reduction across the study population. Figure 2B shows the mean body-weight trajectory with 95% confidence intervals, confirming a sustained and progressive decline throughout follow-up.

Sex-stratified body-weight trajectories are shown in Figure 2C. Both male and female participants exhibited comparable and parallel reductions in body weight over time, indicating that the weight-loss effect associated with biosynthetic semaglutide was consistent across sexes.

Clinically meaningful weight-loss thresholds were achieved by the majority of patients, as shown in Figure 2D. By EOS, 76.5% of patients attained a ≥5% reduction in body weight, while an additional 18.9% achieved 3%–4.9% weight loss. Only 4.6% of patients did not achieve at least a 3% reduction from baseline body weight, indicating a high proportion of responders at the population level.

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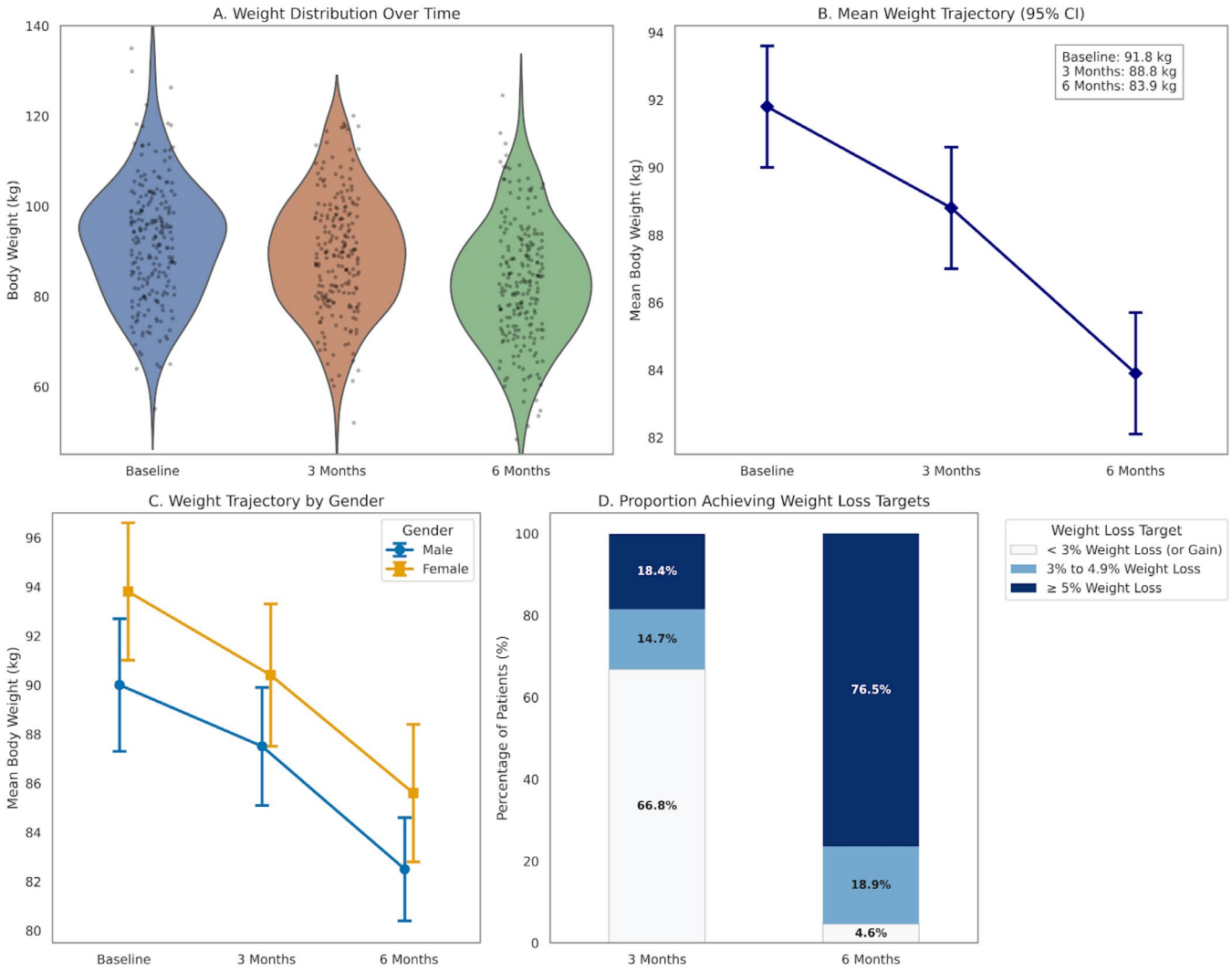


FIGURE 2 | Changes in body weight over time following initiation of biosynthetic semaglutide. (A) Weight distribution over time, (B) mean weight trajectory (95% CI), (C) weight trajectory by gender and (D) proportion achieving weight loss targets.

3.5 | Anthropometric and Central Adiposity Measures

Significant improvements in anthropometric parameters were observed over the 6-month follow-up period among participants with complete paired data ($n = 218$). Body mass index (BMI) demonstrated a consistent and clinically meaningful reduction over time. Mean BMI decreased from $33.61 \pm 6.48\,kg/m^2$ at baseline to $30.74 \pm 6.06\,kg/m^2$ at 6 months, corresponding to a mean absolute reduction of $-2.87\,kg/m^2$ ($p < 0.001$).

Changes in BMI over time are illustrated in Figure S3A,B. It shows the distribution of BMI values at baseline, 3 months, and 6 months using box-and-whisker plots, demonstrating a downward shift of the entire distribution with compression of the interquartile range over time. Figure S3B presents the mean BMI trajectory, confirming a stepwise and sustained decline between baseline, 3 months, and 6 months, supporting a consistent treatment-associated effect across the cohort.

Waist circumference, a marker of central adiposity and cardiometabolic risk, also improved substantially during the study period. Mean waist circumference declined from 103.65 ± 15.71 cm at baseline to 96.93 ± 14.84 cm at 6 months, representing a mean reduction of -6.72 cm ($p < 0.001$).

Corresponding changes in waist circumference are shown in Figure S3C,D. It depicts the distribution of waist circumference at each time point, demonstrating a consistent leftward shift and reduced variability over time. Figure also illustrates the mean waist-circumference trajectory, confirming a progressive reduction from baseline through follow-up, indicative of a sustained decrease in central adiposity across the study population.

3.6 | Sensitivity and ITT Analysis

To evaluate the robustness of the observed clinical improvements and account for potential attrition bias, an ITT analysis was performed on the FAS ($N = 268$) utilising the LOCF imputation method. By carrying forward baseline or intermediate values for patients who discontinued treatment prematurely, this conservative approach inherently dilutes the overall treatment effect size as presented in Table S3.

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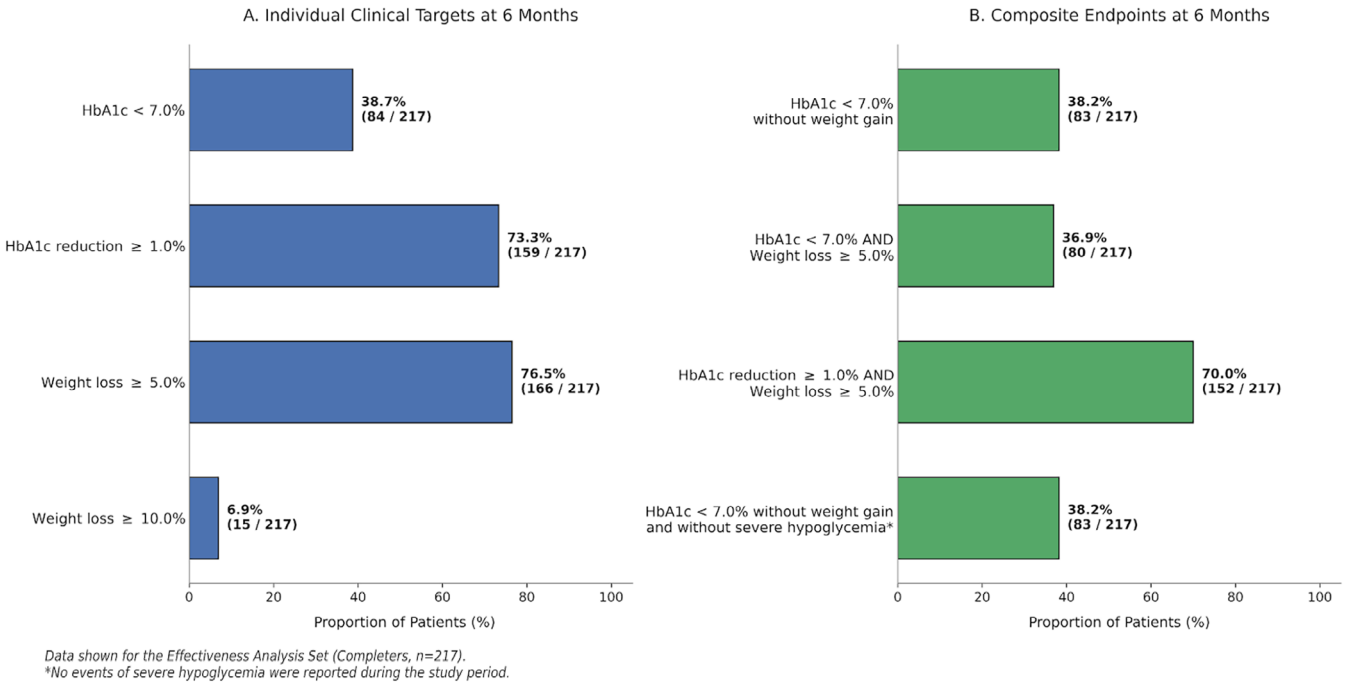


FIGURE 3 | Achievement of individual and composite clinical targets at the end of the study. (A) Individual clinical targets at 6 months and (B) composite endpoints at 6 months.

Despite these stringent imputation parameters, the clinical efficacy of biosynthetic semaglutide remained highly statistically significant. In the ITT-LOCF cohort, the mean HbA1c declined from 9.21% ± 1.49% at baseline to 7.56 ± 1.02% at 6 months, representing an absolute mean reduction of −1.65 ± 1.41% ($p < 0.0001$). Concurrently, mean body weight decreased from 91.76 ± 13.71 kg to 84.84 ± 13.26 kg, yielding a significant mean reduction of −6.92 ± 4.85 kg ($p < 0.0001$).

3.7 | Multivariable Predictors of Glycaemic Response

To address potential confounding and isolate the independent effect of baseline clinical and demographic characteristics on treatment response, a MLR model was constructed. The model predicted the absolute change in HbA1c from baseline to 6 months while simultaneously adjusting for age, sex, baseline HbA1c, baseline BMI, diabetes duration, baseline insulin use, total baseline OAD burden and physical activity level.

The overall regression model demonstrated a strong predictive fit ($R^2 = 0.714$; $F = 63.84$, $p < 0.0001$). The analysis confirmed that the robust glycaemic reductions observed in the cohort were independent of demographic and anthropometric confounders. Specifically, age ($p = 0.831$), sex ($p = 0.224$), baseline BMI ($p = 0.170$), physical activity level ($p = 0.417$) and diabetes duration ($p = 0.258$) were not statistically significant predictors of HbA1c reduction. This indicates that biosynthetic semaglutide provided consistent therapeutic efficacy across diverse patient phenotypes.

Baseline HbA1c emerged as the primary independent predictor of glycaemic change ($\beta = -0.783$, 95% CI: −0.853 to −0.713; $p < 0.001$), corroborating the established clinical paradigm that patients presenting with higher baseline hyperglycaemia experience significantly greater absolute reductions in HbA1c. Additionally, a higher baseline OAD burden was independently associated with a marginally blunted glycaemic reduction ($\beta = +0.130$, 95% CI: 0.016–0.243; $p = 0.025$), reflecting expected clinical dynamics in more advanced, treatment-refractory disease states. These multivariable predictors are detailed in Table S4.

3.8 | Composite Clinical Endpoints

The achievement of clinically relevant individual and composite treatment targets at EOS is summarised in Figure 3. Among patients in the EAS, 38.7% (84/217) achieved HbA1c < 7.0%, while 73.3% (159/217) achieved a reduction in HbA1c of ≥ 1.0%-point from baseline. Weight-loss targets were also frequently achieved, with 93.5% (203/217) attaining ≥ 5% weight loss and 6.9% (15/217) achieving ≥ 10% weight loss (Figure 3A).

Composite cardiometabolic endpoints demonstrated a high proportion of dual responders (Figure 3B). Overall, 36.9% (80/217) of patients achieved both HbA1c < 7.0% and ≥ 5% weight loss, while 70.0% (152/217) achieved both an HbA1c reduction of ≥ 1.0%-point and ≥ 5% weight loss. In addition, 38.2% (83/217) of patients achieved HbA1c < 7.0% without weight gain, and the same proportion achieved HbA1c < 7.0% without weight gain and without any reported severe hypoglycaemic events.

3.9 | Semaglutide Dose Titration and Maintenance

The dose of biosynthetic semaglutide was titrated based on individual patient tolerability and glycaemic response rather than a fixed experimental protocol. When evaluating the final dose distribution across the entire FAS ($N = 268$), the majority of patients successfully tolerated dose escalation to the maximum maintenance

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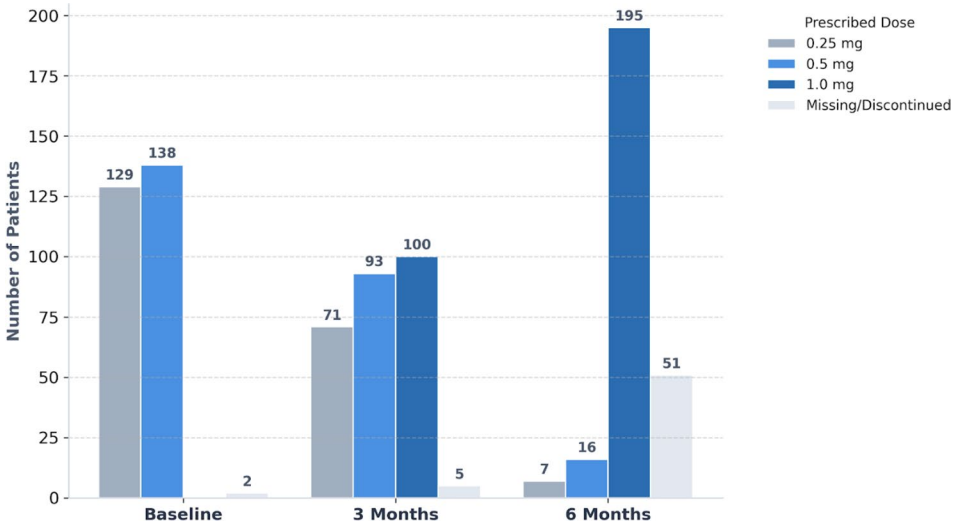


FIGURE 4 | Distribution of prescribed biosynthetic semaglutide doses from baseline to 6 months.

tier. At the 6-month end-of-study visit, 71.6% ($n = 192$) of the total cohort were maintained on the 1.0 mg once-weekly dose. A smaller proportion of patients were maintained on lower doses due to individualised clinical decisions or tolerability thresholds, with 6.0% ($n = 16$) receiving 0.5 mg weekly and 2.6% ($n = 7$) remaining on the 0.25 mg starting dose. The remaining 19.02% ($n = 51$) of the cohort had discontinued treatment or were lost to follow-up prior to the 6-month visit as presented in Figure 4.

Analysis of the titration timelines revealed a pragmatic, deliberate approach to dose escalation. Among patients who escalated therapy, the median time from treatment initiation to achieving the 0.5 mg dose was 64 days. For patients who successfully titrated to the maximal 1.0 mg maintenance dose, the median time to achieve this target was 103 days.

3.10 | Patient-Reported Outcomes

Patient-reported outcomes were assessed in the EAS using validated instruments for treatment satisfaction and health-related quality of life. Adjusted analyses were performed to estimate changes from baseline to 6 months in treatment satisfaction and SF-36v2 physical and mental health summary scores.

Overall, treatment with biosynthetic semaglutide was associated with a significant improvement in treatment satisfaction. After adjustment, the estimated mean increase in Diabetes Treatment Satisfaction Questionnaire status (DTSQs) total score from baseline to 6 months was +7.79 points (95% CI 7.55 to 8.03; $p < 0.0001$; $n = 215$) (Figure S4A).

Improvements were also observed in health-related quality of life. The adjusted mean change in the SF-36v2 physical component summary (PCS) score at 6 months was +21.96 points (95% CI: 21.17–22.76; $p < 0.0001$; $n = 215$), indicating a substantial improvement in physical health status (Figure S4B).

In contrast, the SF-36v2 mental component summary (MCS) score showed a modest but statistically significant change. The adjusted mean change in MCS score from baseline to 6 months was −2.29 points (95% CI: −3.23 to −1.35; $p < 0.0001$; $n = 215$) (Figure S4C).

TABLE 3 | Adverse events reported in ≥ 5% of patients in the safety analysis set (SAS).

Preferred term	Total ($N = 268$), n (%)
Any adverse event	198 (73.9%)
Gastrointestinal disorders	97 (36.2%)
Nausea	52 (19.4%)
Diarrhoea	45 (16.8%)
Headache	54 (20.1%)
General disorders and administration site conditions	47 (17.5%)
Fatigue	47 (17.5%)
Severe hypoglycaemia	0 (0.0%)

Note: Data are number of patients (n) and percentage (%) of patients in the safety analysis set experiencing the event. Only adverse events occurring in ≥ 5% of the SAS are listed. Severe hypoglycaemia was actively monitored, but no events were reported.

3.11 | Safety

3.11.1 | Safety and Adverse Events

During the study period, adverse events (AEs) were reported in 198 patients, with the most frequently observed events being headache ($n = 54$), nausea ($n = 52$), fatigue ($n = 47$) and diarrhoea ($n = 45$). The distribution of the most common adverse events is summarised in Table 3 and illustrated in Figure S5. The majority of AEs were non-serious and consistent with the established tolerability profile of GLP-1 receptor agonists.

Gastrointestinal disorders were the most frequently reported system organ class, affecting 97 patients (36.2%), with nausea and

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diarrhoea being the most common individual events (Table 3). No cases of severe hypoglycaemia were reported during the study. Documented non-severe hypoglycaemic episodes were infrequent.

Permanent discontinuation of study treatment occurred in 34 patients. The most common reason for treatment discontinuation was gastrointestinal adverse effects ($n = 23$). In addition, one patient discontinued treatment due to acute pancreatitis and one patient due to worsening diabetic retinopathy, both of which were considered serious adverse events. Non-adherence ($n = 9$) was also reported as a reason for treatment discontinuation. An overview of treatment completion status in relation to adverse event reporting is shown in Figure S5.

An exploratory evaluation of glycaemic response according to adverse-event severity among study completers is presented in Figure S5. Mean absolute reductions in HbA1c at 6 months were numerically similar across patients reporting mild, moderate or severe adverse events, with no statistically significant differences observed between severity categories ($p = 0.551$).

4 | Discussion

In this prospective, non-interventional real-world study, treatment with biosynthetic semaglutide was associated with clinically meaningful improvements in glycaemic control, body weight, central adiposity and patient-reported outcomes over a 30-week observation period. In parallel, biosynthetic semaglutide demonstrated a safety and tolerability profile consistent with that previously described for semaglutide therapy in both clinical trial and real-world settings, with no new safety signals identified [32–34].

The magnitude of HbA1c reduction observed in this study (−1.86%) is clinically relevant, particularly given the high baseline glycaemic burden and long duration of T2DM in the study population. Larger absolute HbA1c reductions among individuals with higher starting HbA1c levels have been consistently reported across prior clinical and real-world studies of semaglutide, reflecting greater scope for improvement when baseline hyperglycaemia is severe [23, 35, 36]. In line with this, a substantial proportion of patients in the present study achieved guideline-relevant HbA1c targets by end of study, and the majority achieved HbA1c reductions of at least 1.0%, underscoring the clinical significance of these findings [37, 38].

Consistent with its established pharmacological profile, biosynthetic semaglutide was associated with pronounced and sustained reductions in body weight. The mean weight reduction of nearly 8 kg and the high proportion of patients achieving ≥ 5% weight loss are comparable to outcomes reported in the SURE programme and align closely with the weight-loss effects observed in the SUSTAIN trials [35, 39–42].

Reductions in body mass index and waist circumference further support a favourable impact on overall and central adiposity, outcomes of particular relevance given the strong link between obesity, insulin resistance and cardiometabolic risk [43]. Notably, distributional analyses indicated that weight and adiposity reductions were broadly observed across the cohort rather than being driven by a limited subgroup of high responders, reinforcing the generalisability of these effects in routine care [44].

Achievement of composite endpoints combining glycaemic control and weight reduction provides a more integrated assessment of treatment success. In this study, a meaningful proportion of patients achieved combined glycaemic and weight-loss targets, reflecting treatment benefits across multiple cardiometabolic domains. Similar composite outcome patterns have been reported in SURE analyses and support the role of semaglutide-based therapy in addressing contemporary treatment goals that extend beyond glucose lowering alone [45, 46].

Given that baseline OAD burden independently predicted glycaemic response in this cohort, optimising future treatment stratification necessitates the integration of advanced prognostic biomarkers. The serum GPR functions as a robust predictor of all-cause mortality, delineating a critical threshold of metabolic destabilisation [28]. Concurrently, composite inflammatory-nutritional metrics, notably the non-linear association between the neutrophil-to-prognostic-nutritional-index ratio and mortality, provide incremental prognostic resolution beyond conventional cardiometabolic indices [29]. The incorporation of these composite indicators into routine ambulatory care frameworks presents a highly sensitive mechanism for refining cardiovascular risk stratification and characterising phenotypic response variations.

Beyond metabolic outcomes, treatment with biosynthetic semaglutide was associated with marked improvements in patient-reported treatment satisfaction and physical health-related quality of life. Improvements in DTSQs and the SF-36v2 physical component summary mirror findings reported across the SURE programme and highlight the importance of patient-centred benefits in real-world diabetes management [23, 47].

Conversely, the SF-36v2 Mental Component Summary (MCS) score demonstrated a small but statistically significant decline (−2.29 points, $p < 0.0001$) over the 6-month period. Rather than an anomaly, this divergence between physical and mental health domains likely reflects the complex realities of real-world obesity and diabetes management. The decline in MCS may be attributable to several interacting factors. First, the transition to a once-weekly injectable therapy introduces a psychological burden and needle fatigue that is absent with oral antidiabetic regimens. Second, the high incidence of early gastrointestinal adverse events, such as nausea and diarrhoea, can significantly disrupt daily social functioning and psychosocial well-being [48]. Furthermore, because this study reflects routine clinical practice where the intervention is not provided free of charge, the sustained out-of-pocket acquisition costs of biosynthetic semaglutide in a cost-constrained setting likely introduce a continuous element of financial toxicity and psychological stress. Finally, unmet patient expectations regarding the rapidity or magnitude of aesthetic weight loss may blunt the psychological benefit of the therapy, even when objective cardiometabolic targets are successfully achieved. Recognising these mental health impacts is crucial for clinicians, emphasising the need for holistic, ongoing psychological support alongside metabolic treatment [23, 35].

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This divergence between objective physical amelioration and psychological well-being aligns with established methodological frameworks in chronic disease management and intensive therapeutic interventions. Analogous clinical models involving severe physiological stress—including the application of negative pressure wound therapy [49], acellular dermal matrices [50] and technology-assisted anxiolysis in paediatric cohorts [51] consistently demonstrate discrete operational trajectories for physical healing versus patient-centred psychological domains. These parallel findings reinforce the premise that improvements in physical health metrics do not intrinsically confer psychological benefit, necessitating the integration of structured psychosocial support parameters.

The safety profile observed in this study was consistent with the known tolerability of the semaglutide class. Adverse events were predominantly non-serious and most commonly gastrointestinal in nature, as reported in both SURE and SUSTAIN studies [35, 52]. Treatment discontinuation due to adverse events occurred in a minority of patients. Two serious adverse events leading to treatment discontinuation—acute pancreatitis and worsening diabetic retinopathy—were observed, both of which represent recognised risks of GLP-1 receptor agonist therapy. No severe hypoglycaemic episodes were reported, and no new safety signals were identified [46, 52].

Evaluation of the dose escalation trajectory reveals a distinct titration paradox; treatment discontinuation rates peaked during the 0.25 and 0.5 mg initiation phases despite a lower absolute frequency of gastrointestinal events relative to the 1.0 mg maintenance tier. This early-phase attrition corresponds with tolerability bottlenecks documented across broader systemic metabolic interventions, wherein initial side-effect profiles disproportionately dictate long-term therapeutic adherence [53, 54]. While persistence may be stabilised by broader safety-net resources in high-income observational cohorts, initial dose escalation remains the primary barrier to adherence in resource-limited environments. Proactive mitigation of early gastrointestinal symptoms via adjunctive antiemetic prophylaxis or highly individualised, protracted titration protocols provides an actionable clinical mechanism to minimise early attrition.

Contrasting these dose-titration dynamics with high-income observational registries, notably the SemaglUtide Real-world Evidence (SURE) programme, delineates critical systemic disparities in treatment persistence. Whereas the SURE cohorts demonstrate robust adherence trajectories wherein early attrition is predominantly isolated to intractable gastrointestinal intolerance [23, 35], the pronounced early-phase discontinuation observed herein at the 0.25 and 0.5 mg thresholds reflects a compound attrition model. In resource-constrained settings, the initial physiological adaptation phase intersects synergistically with out-of-pocket financial toxicity, artificially amplifying premature discontinuation rates prior to therapeutic optimisation. Nevertheless, despite these early attrition bottlenecks, the ultimate maintenance proportion (71.6% at the 1.0 mg dose) among persisters remains remarkably congruent with the completion metrics reported in high-income SURE registries [35, 36], confirming that upon successful navigation of the initial titration phase, the long-term tolerability and adherence profile of biosynthetic semaglutide directly mirrors that of the innovator molecule.

A key implication of the present findings is their relevance to low- and middle-income and cost-constrained healthcare environments, where access to innovative diabetes therapies is often limited by affordability and availability [55, 56]. The demonstrated effectiveness and tolerability of biosynthetic semaglutide in routine clinical practice suggest that it may represent a pragmatic and potentially more accessible alternative to innovator formulations, without compromising clinical benefit. While formal pharmacoeconomic evaluation was beyond the scope of this study, these real-world data provide an important clinical foundation for future cost-effectiveness analyses in resource-limited settings.

Beyond pharmacotherapy, comprehensively addressing chronic disease burden requires evaluating systemic metabolic stabilisers, such as anabolic agents in catabolic states [57], alongside a broader adoption of technology-enabled interventions. Just as recent systematic reviews and meta-analyses have demonstrated the efficacy of technology-assisted pain management [53] and virtual reality in specialised settings like paediatric burn care [51], the integration of digital health tools alongside semaglutide therapy represents a critical frontier for maximising patient-reported outcomes and long-term adherence.

4.1 | Strengths and Limitations

Strengths of this study include its prospective design, real-world setting, inclusion of patient-reported outcomes and comprehensive assessment of metabolic and safety endpoints. Several limitations should be considered when interpreting the findings. First, the observational, single-arm design lacks a concurrent comparator group, limiting definitive causal inference. In routine clinical care, unmeasured confounders such as concurrent lifestyle modifications or regression to the mean may contribute to the observed outcomes. Nevertheless, the cardiometabolic improvements achieved in this cohort align closely with the established efficacy profile of semaglutide seen in larger global clinical trials and real-world registries.

Second, treatment discontinuation and missing data are inherent to real-world studies. The attrition observed in this cohort reflects the practical, real-world barriers of out-of-pocket healthcare costs and the physiological adaptation required during early dose titration, though baseline comparability across the cohort suggests a low risk of selection bias. Finally, while the 30-week follow-up adequately captures the dose-titration and early maintenance phases, longer-term outcomes beyond this period were not assessed.

A notable limitation is the generalisability of these findings to underserved populations in LMICs. First, recruiting from specialised urban centres yielded a cohort with better baseline healthcare access than the average patient. Second, the prerequisite for documented baseline HbA1c assumes reliable laboratory monitoring, which is frequently deficient in rural areas. Finally, despite reduced acquisition costs, sustained out-of-pocket expenses present significant financial toxicity. In lower-income

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demographics, these cumulative costs will likely precipitate higher treatment attrition than observed here, potentially limiting the intervention's real-world scalability in fully resource-constrained environments.

4.2 | Clinical Implications

This real-world study demonstrates that biosynthetic semaglutide delivers clinically meaningful improvements in glycaemic control, body weight and patient-reported outcomes, with a safety profile consistent with established semaglutide therapy. The alignment of these findings with results from the SURE real-world programme and the SUSTAIN clinical trials supports the robustness and generalisability of the observed benefits. In cost-constrained and resource-limited health-care settings, biosynthetic semaglutide may represent a valuable option for delivering comprehensive cardiometabolic risk reduction in routine diabetes care.

Author Contributions

All authors and investigators made substantial contributions to the conception, design, conduct, analysis and reporting of this study in accordance with their respective roles. Data integrity, statistical analyses and interpretation were conducted independently by the academic research team. The findings presented in this manuscript reflect the authors' scientific judgement and are free from sponsor influence.

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Ethics Statement

Ethical approval for this study has been obtained from the Human Research Ethics Committee (Approval Number: USM/JEPeM/PP/25040370), National Bioethics Committee Pakistan (NBCR-1286), along with the Northwest General Hospital, Peshawar, Alliance Healthcare Pvt. Ltd. IRB & Ethics Committee (Reference: IRB&EC/2025-GH/0228). The study is registered with the Australian New Zealand Clinical Trials Registry under the identifier ACTRN12625000610437. All procedures will be conducted in accordance with Good Clinical Practice and the ethical standards of the Declaration of Helsinki.

Conflicts of Interest

Dr. Arshad Hussain has received honoraria for delivering educational lectures from BF BioSciences. The funding organization provided support for the conduct of this study but had no role in the study design; data collection, analysis, or interpretation; manuscript preparation; or the decision to submit the manuscript for publication. All other authors declare that they have no competing financial or non financial interests.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.71043.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Geographic distribution of study sites and participant recruitment across Pakistan. **Figure S2:** Patient disposition and study flow. **Table S1:** Baseline characteristics of study completers vs. non-completers. **Table S2:** Distribution and de-escalation of concomitant antihyperglycemic therapies from baseline to 6 months. **Figure S3:** Changes in body mass index (BMI) and waist circumference over time following initiation of biosynthetic semaglutide. **Table S3:** Intention-to-treat (ITT) analysis of glycaemic and weight outcomes using last observation carried forward (LOCF). **Table S4:** Multivariable linear regression predicting absolute change in HbA1c at 6 months. **Figure S4:** Adjusted changes in patient-reported outcomes from baseline to 6 months. **Table S5:** Incidence of specific gastrointestinal events and treatment discontinuation stratified by maximum tolerated dose ($N = 268$). **Figure S5:** Adverse events, study retention and association with glycaemic response.

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