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Review Article

Semaglutide as an Antidiabetic Medication: A Summary of the Evidence from the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes Clinical Trial Program

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Abstract: *Background*: The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trial program was a phase III, multinational, multicenter program comprising 13 trials. *Objective*: Investigate the safety and efficacy of once-weekly, subcutaneous semaglutide versus other antidiabetic comparators, both as a monotherapy and in addition to other antidiabetic medications. *Methods*: This review summarizes the 10 trials that comprise the bulk of the evidence which led to FDA approval of semaglutide as an antidiabetic drug. Most articles were accessed via the National Center for Biotechnology Information database using pertinent search terms. *Results*: Semaglutide 0.5 mg and 1 mg weekly subcutaneous injection led to HA1c reductions by 1.1%–1.5% and 1.5%–1.8%, respectively. Bodyweight reduction with 0.5 mg and 1 mg dose of semaglutide ranged from 3.47–4.6 kg and 4.53–6.5 kg, respectively. SUSTAIN 6, in particular, found cardiovascular risk factor benefits, including the rate of nonfatal myocardial infarction, cardiovascular death and nonfatal strokes in high-risk patients correlated with the use of semaglutide in patients with type 2 diabetes. *Conclusions*: Semaglutide is superior to other glucagon-like peptide-1 receptor agonists, including exenatide, dulaglutide, and liraglutide in hemoglobin A1c reduction. It is also helpful for chronic weight loss and has cardioprotective effects.

Keywords: Semaglutide, SUSTAIN, Incretin Therapy, GLP-1 Analog, Antidiabetic Therapy, Type Two Diabetes

1. Introduction

Incretin-based therapies are used to treat type 2 diabetes and target the receptors of endogenous glucagon-like peptide-1 (GLP-1) [1]. Both dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists (GLP-1 RAs) are included in this category, [2] but exert their effects via different strategies [1]. DPP-4 inhibitors inhibit the activity of the endogenous DPP-4 enzyme, which breaks down plasma incretins [3]. GLP-1 RAs stimulate endogenous GLP-1 receptors [3]. Incretin-based therapies reduce plasma glucose without hypoglycemia [1], making them a preferred treatment for combating elevated blood glucose in treating type 2 diabetes. In addition, GLP-1 RAs reduce the overall incidence of major adverse cardiovascular events in patients and are related to the reduction of appetite and subsequent weight loss [2, 4]. According to the American Diabetes Association (ADA) and the current American Association of Clinical Endocrinologist guidelines, GLP-1 RAs have been accepted for use as a secondary treatment add-on to metformin monotherapy [4, 5].

Semaglutide is a relatively new GLP-1 RA approved as an antidiabetic medication under the trade name Ozempic. Semaglutide shares a 53% homology with endogenous GLP-1 with key modifications, including the substitution of alanine for α-aminoisobutyric acid at position 8 and an addition of a fatty diacid chain at position 26 [6]. These modifications result in an increased half-life of the molecule, allowing for administration via subcutaneous injection once weekly. Phase II clinical trials investigating the safety and efficacy of

semaglutide demonstrated promising results in outcomes of glycemic control and bodyweight reduction that were dose-dependent [7]. At the end of phase II, 0.5 mg and 1.0 mg doses with a 4-week dose-escalation period advanced to the phase III SUSTAIN clinical trial program [1]. This paper is the first and only to summarize data relating to the safety and efficacy of SC semaglutide from the first 10, randomized, multicenter trials comprising the SUSTAIN clinical trial program.

2. Methods

The following summary was formulated based on a database search for pertinent literature. Search via the U.S. National Library of Medicine Clinical Trials database applying the search criteria of "diabetes" and "semaglutide" yielded 599 total results. However, only thirteen SUSTAIN trials were selected because these were original, randomized, controlled clinical trials done before approval of injectable semagluitde for management of diabetes.

Three of the original thirteen studies, including SUSTAIN CHINA MRCT, SUSTAIN (Japan), and SUSTAIN (Japan, sitagliptin), were excluded from this summary due to the redundancy of their comparators. SUSTAIN CHINA MRCT compared semaglutide to sitagliptin, as did SUSTAIN (Japan, sitagliptin). Sitagliptin was already compared to semaglutide during SUSTAIN 1–10. SUSTAIN (Japan) compared semaglutide to any oral antidiabetic medication, which can include dipeptidyl peptidase-4 inhibitors, biguanides, sulfonylureas, glinides, α-glucosidase inhibitors, or thiazolidinediones. Biguanides, sulfonylureas, and thiazolidinediones were each compared at least once in SUSTAIN 2–5 and 7–10 [6, 8-16].

The studies making up the present review encompass a period from 2017 to 2020 [6, 14]. Other pertinent literature for this review was obtained primarily from a search via the National Center for Biotechnology Information database. Search terms used included "semaglutide," "incretin therapies," "Ozempic," and "diabetes mellitus type 2."

2.1. Design

The SUSTAIN clinical trial program was designed to test the safety and efficacy of once-weekly SC semaglutide. Each of the 10 total trials were randomized and controlled by either placebo [8-11] or active agent [6, 12-16]. The trials compared the efficacy and safety of semaglutide versus multiple antidiabetic comparators, including insulin glargine [6], sitagliptin [13], exenatide [12], dulaglutide [16], canagliflozin [15], and liraglutide [14]. While SUSTAIN 1, 2, 5, 6, 8, and 9 were all double-blind studies [8-11, 13, 15], this was not always attainable due to differences in the patented devices used to administer certain comparators, routes of administration, and dosing methods for certain comparators [6, 12, 14, 16]. All 10 trials of the SUSTAIN program were conducted as multicenter and multinational studies spanning five continents, except Australia and Antarctica.

2.2. Patients

Most studies in the SUSTAIN clinical trial program had a patient population comprising 18 years or older, except for SUSTAIN 6, which studied the cardiovascular risk factors of semaglutide in patients 50 years or older [8]. All of the SUSTAIN trials required patients with type 2 diabetes to have an HA1c of at least 7.0%. The upper HA1c limit varied across trials, with many cutting off at an HA1c of 10.5% [12, 13, 15, 16]. Others had a cut off of either 10.0% [6, 9-11] or 11.0% [14], while SUSTAIN 6 had no upper limit exclusion [8]. SUSTAIN 6 also required patients with a history of cardiovascular disease to investigate cardiovascular risk.

Except for SUSTAIN 1, trials surveyed a wide variety of treatment backgrounds. SUSTAIN 2–10 allowed the use of metformin, either by itself [15, 16] or in combination with other antidiabetic agents, including thiazolidinediones [8, 12, 13], sulfonylureas [6, 8, 11, 12], or SGLT2 inhibitors [8, 11, 14]. SUSTAIN 5 and SUSTAIN 9 investigated semaglutide as an add-on to basal insulin and an SGLT2 inhibitor, respectively, either alone or combined with metformin [9, 11]. SUSTAIN 1 included patients with type 2 diabetes managed with lifestyle modifications only [10].

Other exclusion factors pertained to family or personal histories. Patients with a personal or family history of chronic or idiopathic acute pancreatitis, thyroid carcinoma, or MEN syndrome type 2 were excluded [10]. Several trials also required an eGFR of>30 [6, 9, 10, 14] or>60 [11-13, 16] Cardiovascular events, such as stroke, heart failure, or acute coronary event occurring 90 days prior to the start of treatment also resulted in excluding patients [6, 8, 10-13, 15, 16].

2.3. Comparators, Doses, and Duration

Following phase II clinical trials, semaglutide was approved to be administered at doses of 0.5 mg and 1.0 mg [1]. Both doses were compared with a placebo in SUSTAIN 1 and SUSTAIN 5 for 30 weeks [9, 10] and SUSTAIN 6 for 104 weeks [8]. SUSTAIN 9 also compared the 1.0 mg dose to treatment with placebo for 30 weeks [11]. The 0.5 mg and 1.0 mg doses were also compared with oral sitagliptin (100 mg) for 56 weeks [13], insulin glargine (sliding scale) for 30 weeks [14], and dulaglutide (0.75 mg, 1.5 mg) for 40 weeks [16], Trials comparing semaglutide with exenatide (2 mg), canagliflozin (300 mg), and liraglutide (1.2 mg) for 56, 52, and 30 weeks, respectively, were only compared with a 1.0 mg dose [12, 14, 15].

3. Results

3.1. Glycemic Control

All 10 clinical trials comprising the SUSTAIN clinical trial program found significant glycemic control benefits using SC semaglutide (Table 1). For patients receiving 0.5 mg SC semaglutide, HA1c reductions ranged from 1.1%–1.5% [8, 16]. For patients receiving the 1.0 mg dose, reductions ranged from 1.5%–1.8% [9, 11, 12, 15, 16]. Compared to other

GLP-RAs, semaglutide exhibited a superior reduction of HA1c (Table 1). SUSTAIN 3 found semaglutide 1.0 mg reduced HA1c by 1.5% while exenatide showed average reductions of 0.9% [12]. In SUSTAIN 7, dulaglutide showed a reduction of 1.1% for a 0.75 mg dose, while semaglutide 0.5 mg showed a reduction of 1.5%. SUSTAIN 7 also found a reduction of 1.4% for a 1.5 mg dose of dulaglutide and 1.8% reduction for 1.0 mg semaglutide [16]. Liraglutide was also outperformed by semaglutide, showing reductions of 1.0% versus 1.7% for a 1.0 mg dose of semaglutide [14]. When given as a monotherapy, SC semaglutide was able to reduce HA1c on average by 1.45% (0.5 mg) and 1.55% (1.0 mg) [10]. When added to metformin, semaglutide's effectiveness in lowering HA1c seems to be improved, especially with 1.0 mg doses [6, 9. 13. 14. 16]. SUSTAIN 6, which lasted for 104 weeks, found reductions of 1.1% (0.5 mg) and 1.4% (1.0 mg), suggesting SC semaglutide is agreeable for long-term use, as far as efficacy in lowering HA1c is concerned (Table 1) [8].

Fasting plasma glucose (FPG) was also collected throughout each of the clinical trials. SC semaglutide was found to successfully reduce FPG by a greater magnitude than comparators (Table 1). A 0.5 mg dose of semaglutide showed reductions in FPG ranging from 1.6–2.51 mmol/L [9, 10], while a 1.0 mg dose showed reductions ranging from 2.2–2.8 mmol/L [11, 12, 16]. As a monotherapy, SC semaglutide showed FPG reductions of 2.51 mmol/L (0.5 mg) and 2.34 mmol/L (1.0 mg). These reductions only seem to improve when we see semaglutide added as a secondary treatment to metformin monotherapy [6, 13, 16].

Glycemic control was also monitored by recording the percent of the patient populations achieving an HA1c of≤7% and ≤6.5%. The achievement of an HA1c of≤7% is recommended by the ADA for patients with type 2 diabetes, as evidence suggests this reduces the risk of developing microvascular complications due to hyperglycemia [17]. For patients treated with a 0.5 mg dose of SC semaglutide, 57%–74% achieved this goal [6, 10]. This range is even more inclusive for patients on 1.0 mg semaglutide, with 66%–80% achieving an HA1c of ≤7% (Table 1) [14, 15]. The percentage of patients with HA1c of ≤6.5% on 0.5 mg semaglutide ranged from 37%–59% [6, 10] and 47%–67% on 1.0 mg semaglutide [12, 16]. The achievement of an HA1c of ≤7% without severe or blood glucose (BG) confirmed hypoglycemia was also evaluated. This was achieved by 47%–66% of patients on 0.5 mg semaglutide [6, 10] and 56%–76% of patients on 1.0 mg semaglutide [12, 14]. These findings were either non-inferior or superior to their comparators (Table 1).

Table 1. *Summary of the SUSTAIN Results.*

Trial (# of Participants)	**SUSTAIN 1 (N=388) [10]**		**SUSTAIN 2 (N=1231) [13]**		**SUSTAIN 3 (N=809) [12]**		**SUSTAIN 4 (N=1089) [6]**		**SUSTAIN 5 (N=397) [9]**	
Background Regimen (alone or in combination with one another)	Diet and Exercise		Metformin, Pioglitazone, Rosiglitazone		Metformin, Sulfonylurea, Thiazolidinedione		Metformin, Sulfonylurea		Metformin, Basal Insulin	
Duration (weeks)	30		56		56		30		30	
Comparators	Sema	Placebo	Sema	Sitagliptin	Sema	Exenatide XR	Sema	Insulin Glargine	Sema	Placebo
Doses (mg)	0.5, 1.0		0.5, 1.0	100	1.0	2.0	0.5, 1.0		0.5, 1.0	
Mean change from baseline										
HA1c (%)	−1.45*, −1.55*	−0.02	−1.3*, −1.6*	−0.5	−1.5*	−0.9	−1.21*, −1.64*	−0.83	−1.4*, −1.8*	−0.1
FPG (mg/dL)	−2.51*, −2.34*	−0.55	−2.1*, −2.6*	−1.1	−2.2*	−1.5	−2.04, −2.73*	−2.12	−1.6*, −2.4*	−0.5
Bodyweight (kg)	−3.73*, −4.53*	−0.98	−4.3*, −6.1*	−1.9	−5.6*	−1.9	−3.47*, −5.17*	1.15	−3.7*, −6.4*	−1.4
BMI (kg/m2)	−1.36*, −1.23*	−0.38	−1.6*, −2.3*	−0.7	−2.0*	−0.6	−1.23*, −1.85*	0.42	NR	NR
Proportion achieving thresholds (%)										
HA1c ≤7.0	74*, 72*	25	69*, 78*	36	67*	40	57*, 73*	38	61*, 79*	11
HA1c ≤6.5	59*, 60*	13	53*, 66*	20	47*	22	37*, 54*	18	41*, 61*	5
HA1c ≤7.0 w/o hypoglycemia	66*, 65*	19	63*, 74*	27	56*	28	47*, 64*	16	54*, 67*	7
Bodyweight loss of >5%	37*, 45*	7	46*, 62*	18	52*	17	37*, 51*	5	42*, 66*	11
Bodyweight loss of >10%	8*, 13*	2	13*, 24*	3	21*	4	8*, 16*	2	9*, 26*	3

Trial (# of Participants)	**SUSTAIN 6 (N=3297) [8]**	**SUSTAIN 7 (N=1201) [16]**	**SUSTAIN 8 (N=788) [15]**	**SUSTAIN 9 (N=302) [11]**	**SUSTAIN 10 (N=577) [14]**
Background Regimen (alone or in combination with one another)	0−2 antihyperglycemic agents	Metformin	Metformin	Metformin, Sulfonylurea, SGLT-2 inhibitor	Metformin, SGLT-2 inhibitor
Duration (weeks)	104	40	52	30	30

Trial (# of Participants)	**SUSTAIN 6 (N=3297) [8]**		**SUSTAIN 7 (N=1201) [16]**		**SUSTAIN 8 (N=788) [15]**		**SUSTAIN 9 (N=302) [11]**		**SUSTAIN 10 (N=577) [14]**	
Comparators	Sema	Placebo	Sema	Dula	Sema	Canagliflozin	Sema	Placebo	Sema	Lira
Doses (mg)	0.5, 1.0		0.5, 1.0	0.75, 1.5	1.0	300	1.0		1.0	1.2
Mean change from baseline										
HA1c (%)	−1.1*, −1.4*	−0.4, −0.4	−1.5*, −1.8*	−1.1, −1.4	−1.5*	−1.0	−1.5*	−0.1	−1.7*	−1.0
FPG (mg/dL)	NR	NR	−2.2, −2.8*	−1.9, −2.2	−2.3*	−2.0	−2.2*	0.0	−2.7*	−1.5
Bodyweight (kg)	−3.6*, −4.9*	−0.7, −0.5	−4.6*, −6.5*	−2.3, −3.0	−5.3*	−4.2	−4.7*	−0.9	−5.8*	−1.9
BMI (kg/m^2)	NR	NR	−1.6*, −2.3*	−0.8, −1.1	−2*	−1.5	−1.7*	−0.3	−2*	−0.7
Proportion achieving thresholds (%)										
HA1c ≤7.0	NR	NR	68*, 79*	52, 67	76*	51	79*	19	80*	46
HA1c ≤6.5	NR	NR	49*, 67*	34, 47	62*	27	56*	4	58*	25
HA1c ≤7.0 w/o hypoglycemia	NR	NR	64*, 74*	44, 58	70*	45	69*	16	76*	37
Bodyweight loss of >5%	NR	NR	44*, 63*	23, 30	53	47	50*	8	56*	18
Bodyweight loss of >10%	NR	NR	14*, 27*	3, 8	23*	9	15*	1	19*	4

This table summarizes the primary and secondary endpoints of the SUSTAIN clinical trial program, including the changes seen in HA1c, FPG, bodyweight, BMI, and the proportion of patients achieving thresholds such as an HA1c ≤ 7.0%, 6.5%, and 7.0% without severe hypoglycemia, as well as bodyweight reductions of>5% and 10%.

* $P < 0.05$, indicating the superiority of semaglutide versus the respective comparator

NR This value was not recorded in the trial results

Abbreviations: Sema (semaglutide), Dula (dulaglutide), Lira (liraglutide), FPG (Fasting Plasma Glucose), BMI (body mass index), HA1c, (hemoglobin A1c),

References: Aroda VR et al. [6], Marso SP et al. [8], Rodbard HW et al. [9], Sorli C et al. [10], Zinman B et al. [11], Ahmann AJ et al. [12], Ahrén B et al. [13], Capehorn MS et al. [14], Lingvay I et al. [15], Pratley RE et al. [16].

3.2. Bodyweight Reduction

Similar to other GLP-1 RAs, semaglutide has been successful in promoting weight loss in patients. On the 0.5 mg dose of SC semaglutide, bodyweight reduction ranged from 3.47–4.6 kg [6, 16], while on the 1.0 mg dose, bodyweight reduction ranged from 4.53–6.5 kg (Table 1) [10, 16]. BMI was also reduced for both doses, ranging from reductions of 1.23–1.6 kg/m^2 (0.5 mg) and 1.23–2.3 kg/m^2 (1.0 mg) (Table 1) [10, 13, 16]. All patients, independent of the comparator they were placed on, experienced weight loss. The only exception to this was those patients treated with insulin glargine alone in SUSTAIN 4, who showed a weight gain of 1.15 kg (Table 1) [6]. The weight loss experienced by those using semaglutide was non-inferior or superior to its comparator, including other antidiabetic medications known to cause weight loss.

Other existing GLP-1 RAs were found to be inferior to semaglutide in bodyweight reduction (Table 1). During SUSTAIN 3, exenatide showed an average bodyweight reduction of 1.9 kg, versus semaglutide 1.0 mg, which showed an average weight loss of 5.6 kg [12]. Similarly, in SUSTAIN 7, dulaglutide showed an average bodyweight reduction of 2.3 kg for its lower dose of 0.75 mg, compared to 0.5 mg semaglutide, which had an average decrease of 4.6 kg. Higher doses of dulaglutide also failed to outperform semaglutide, with 1.5 mg dulaglutide showing an average reduction of 3.0 kg versus 1.0 mg semaglutide with an average reduction of 6.5 kg [16]. Patients on liraglutide during SUSTAIN 10 had an average bodyweight reduction of 1.9 kg compared to 5.8 kg for 1.0 mg semaglutide [14]. SGLT2 inhibitors, which are also known to cause weight loss, were compared with semaglutide during SUSTAIN 8. Canagliflozin was the chosen representative for this drug class and was found to reduce 4.2 kg, while semaglutide 1.0 mg showed a reduction of 5.3 kg [15].

When given as a monotherapy, semaglutide showed bodyweight reductions of on average 4.3 kg (0.5 mg) and 6.1 kg (1.0 mg). When added to metformin monotherapy, semaglutide's efficacy at lowering bodyweight improved (Table 1) [6, 10, 12-16]. This was also observed when semaglutide was added to an SGLT-2 inhibitor, as demonstrated in SUSTAIN 9 [11]. Also promising is the fact that semaglutide was still able to promote weight loss in patients also taking basal insulins. As was observed in SUSTAIN 4, which investigated insulin glargine, basal insulins are known to cause weight gain [6, 18]. When semaglutide was added to treatment with basal insulin in SUSTAIN 5, weight reductions of 3.7 kg (0.5 mg) and 6.4 kg (1.0 mg) were still found [10].

Other weight loss parameters that were investigated include the percentage of patients achieving a weight loss of at least 5% and at least 10%. Weight loss of at least 5% is known to be clinically significant, as this can reduce cardiovascular risk factors [19]. Around 37%–46% of patients taking semaglutide 0.5 mg once-weekly were able to achieve a weight loss of at least 5% [6, 10, 13], and 8%–14% were able to reduce their weight by at least 10% (Table 1) [6, 10, 16]. Around 45%–66% of patients taking semaglutide 1.0 mg were able to achieve a weight loss of at least 5% [9, 10], and 12%–27% were able to achieve a weight loss of at least 10% [10, 16]. These findings showed that semaglutide was superior at achieving these parameters in all but SUSTAIN 8, which failed to establish a significant difference between semaglutide and canagliflozin as far as the percentage of patients able to achieve a weight loss of at least 5% (Table 1).

3.3. Quality of Life and Safety

Around 64%–89.6% of patients reported adverse events with 0.5 mg semaglutide treatment [8, 10], resulting in discontinuation in 4.5%–11.5% of patients (Table 2) [8, 9]. Around 38%–50.7% of patients in the 0.5 mg treatment groups experienced gastrointestinal (GI) adverse events, making this the most prevalent adverse event type recorded (Table 2) [8, 10]. Most GI events were categorized as mild (30%–37%) [10, 13] or moderate (10%–15%) [6, 10]. Only around<1%–3% were considered severe [10, 13, 16]. GI events led to discontinuation of the 0.5 mg semaglutide treatment in 4%–7% of patients (Table 2) [10, 13]. As for the 1.0 mg treatment groups, 56%–89.1% of patients experienced an adverse event and 5%–14.5% of these resulted in discontinuation [8, 10]. Around 37.3%–52.3% of patients in the 1.0 mg treatment groups experienced GI adverse events [8, 11], most of which were mild (30.7%–38%) [6, 11, 16] or moderate (12%–16%) [13, 16] Only 1.3%–3% of GI adverse events were considered severe [11, 13, 16]. Around 3%–8% of these events resulted in discontinuation by the patient (Table 2) [10, 13].

Patients with a history of idiopathic acute or chronic pancreatitis are not recommended to take semaglutide. Significant increases in pancreatic lipase were identified throughout the SUSTAIN clinical trial program [9]. Around 6%–8% of patients in the 0.5 mg treatment groups experienced lipase increases [10, 13] as did 4%–10.1% of patients in the 1.0 mg groups [10, 12]. Three confirmed acute pancreatitis cases were identified in the 0.5 mg treatment group of SUSTAIN 2 and chronic pancreatitis was confirmed in one patient in the 1.0 mg treatment group [13]. One patient with a confirmed metastatic pancreatic carcinoma was identified in SUSTAIN 5, 65 days post-treatment [9]. A higher incidence of retinopathy complications, including vitreous hemorrhage and blindness, was reported in patients treated with semaglutide compared to placebo. [8] This was considered related to the rapidity and magnitude of glycemic improvement rather than the direct side effect of semaglutide.

The SUSTAIN program found semaglutide to have cardioprotective properties [8, 20]. SUSTAIN 6 specifically investigated patients' cardiovascular outcomes with cardiovascular disease history, taking 0.5 mg or 1.0 mg SC semaglutide. Over the course of 104 weeks, 6.6% of patients had fatal cardiovascular events versus 8.9% in the placebo groups [8]. SUSTAIN 2 also found one cardiovascular-related fatality in the 0.5 mg treatment group and one cardiorespiratory fatality in the 1.0 mg treatment group [13]. Three cardiovascular-related fatalities were reported in SUSTAIN 4 [6].

SUSTAIN 6 saw 2.9% of patients experience a nonfatal myocardial infarction and 1.6% experience a nonfatal stroke versus 3.9% and 2.7% in the placebo groups, respectively [8]. Overall, there were significantly lower rates of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients taking semaglutide versus those taking a placebo. Around 1%–9.1% of patients taking semaglutide 0.5 mg had nonfatal cardiovascular events during the other remaining SUSTAIN trials, and only 1%–5.3% of patients taking semaglutide 1.0 mg [6, 9, 16]. In addition, significant pulse rate increases were observed in patients taking semaglutide [6, 9, 10, 15]. This is a common side effect of GLP-1 RAs as a drug class and should be considered with patient cardiovascular history when prescribing semaglutide [21].

Throughout the SUSTAIN clinical trial program, severe hypoglycemia reports were relatively low [9-12, 15, 16]. The most significant observed rates were found during SUSTAIN 6, which saw 23.1% of patients experience severe hypoglycemia in the 0.5 mg treatment group and 21.7% in the 1.0 mg treatment group (Table 2) [8]. However, these results were not significantly different from those of the placebo groups. Low risk of hypoglycemia is a known property of GLP-1 RAs, as they are incretin-based therapies [7]. Overall treatment satisfaction was significantly improved during several of the SUSTAIN trials [6, 9, 11, 13].

Table 2. *Summary of the SUSTAIN Safety Outcomes.*

Trial (# of Participants)	Doses and Comparators	Percent Of AEs	Percent Discontinuation Due to AEs	Percent GI AEs: Severe, Moderate, Mild	Percent Discontinuation Due to GI AEs	Severe or BG-Confirmed Hypoglycemia
SUSTAIN 1 (N=388) [10]	SC semaglutide 0.5 mg	64	6	38: <1, 15, 30	4	
	SC semaglutide 1.0 mg	56	5	38: 2, 13, 32	3	None
	Placebo	53	2	15: 0, 4, 12	<1	
SUSTAIN 2 (N=1231) [13]	SC semaglutide 0.5 mg	75	8	44: 3, 14, 37	7	
	SC semaglutide 1.0 mg	71	10	40: 3, 12, 35	8	NR
	Sitagliptin 100 mg	72	3	24: 1, 5, 20	3	
SUSTAIN 3 (N=809) [12]	SC semaglutide 1.0 mg	75	9	NR	NR	2 events*
	Exenatide XR 2 mg	76	7			
SUSTAIN 4 (N=1089) [6]	SC semaglutide 0.5 mg	70	6	41: 2, 10, 36	3	
	SC semaglutide 1.0 mg	73	7	43: 2, 14, 38	5	NR
	Insulin glargine	65	1	15: 1, 4, 12	0	
SUSTAIN 5 (N=397) [9]	SC semaglutide 0.5 mg	69	5			8%
	SC semaglutide 1.0 mg	64	6	NR	NR	11%
	Placebo	58	<1			
SUSTAIN 6 (N=3297) [8]	SC semaglutide 0.5 mg	90	12	51		23%
	SC semaglutide 1.0 mg	89	15	52	NR	22%
	Placebo	91	6	36		22%
	Placebo	89	8	35		21%

Trial (# of Participants)	Doses and Comparators	Percent Of AEs	Percent Discontinuation Due to AEs	Percent GI AEs: Severe, Moderate, Mild	Percent Discontinuation Due to GI AEs	Severe or BG-Confirmed Hypoglycemia
SUSTAIN 7 (N=1201) [16]	SC semaglutide 0.5 mg	68	8	43: 3, 13, 36	5	3%
	Dulaglutide 0.75 mg	62	5	33: 1, 7, 28	2	1%
	SC semaglutide 1.0 mg	69	10	44: 2, 16, 38	6	2%
	Dulaglutide 1.5 mg	74	7	48: 3, 13, 42	5	2%
SUSTAIN 8 (N=788) [15]	SC semaglutide 1.0 mg	76	10	47	7	2%
	Canagliflozin 300 mg	72	5	28	1	1%
SUSTAIN 9 (N=302) [11]	SC semaglutide 1.0 mg	69	9	37: 1, 14, 31	7	11%
	Placebo	60	2	13: 0, 3, 11	0	2%
SUSTAIN 10 (N=577) [14]	SC semaglutide 1.0 mg	71	11	44	7	NR
	Liraglutide 1.2 mg	66	7	38	4	

This table summarizes the safety outcomes of the SUSTAIN clinical trial program, including the overall percentage of adverse events; the percentage of GI-related adverse events; and whether these were considered severe, moderate, or mild; and the percentage of discontinuations due to said events. Also included is the number or percent of severe or BG-confirmed hypoglycemia.

*The two events of "Severe or BG-confirmed Hypoglycemia" during SUSTAIN 3 were both in the SC semaglutide 1.0 mg group.

NR This value was not recorded in the trial results

Abbreviations: AE (Adverse Events), GI (Gastrointestinal), BG (Blood Glucose)

References: Aroda VR et al. [6], Marso SP et al. [8], Rodbard HW et al. [9], Sorli C et al. [10], Zinman B et al. [11], Ahmann AJ et al. [12], Ahrén B et al. [13], Capehorn MS et al. [14], Lingvay I et al. [15], Pratley RE et al. [16].

4. Discussion

According to trial results, semaglutide is superior to the other available antihyperglycemic agents currently on the market at reducing HA1c and bodyweight [6, 8-16]. This is incredibly encouraging because semaglutide has a similar safety profile to other GLP-1 RAs, with most adverse events being GI-related and mild to moderate in severity [6, 8-16]. GLP-1 RAs, including semaglutide, also have cardioprotective properties [8, 20] and a low risk of hypoglycemia [7, 10].

Compared to other GLP-1 RAs, semaglutide has demonstrated superiority in both lowering HA1c and reducing bodyweight in patients with type 2 diabetes (Table 1) [12, 14, 16]. Providers now have an additional agent that may perform superiorly to previously administered GLP-1 Ras [3, 4, 5, 7]. Other antihyperglycemic agents that are known to cause weight loss, such as SGLT-2 inhibitors [18], and weight neutral antihyperglycemic agents, such as DPP-4 inhibitors [22], were also outperformed in both the reduction of HA1c and bodyweight throughout the SUSTAIN program [13, 15]. These findings are substantial because obesity/overweight are typically comorbid with type 2 diabetes [23], and weight loss in patients with type 2 diabetes can lower HA1c [19, 24].

Biguanides, like metformin, are typically one of the first pharmacological interventions received by patients with type 2 diabetes in the clinical setting due to their low risk of hypoglycemia, antihyperglycemic properties, and moderate weight loss effects [5, 25]. When semaglutide was added to metformin monotherapy during the SUSTAIN trials, the weight loss experienced by patients increased in magnitude when compared to taking either agent alone [6, 9, 12-16]. Similar effects were found after the addition of semaglutide to treatment with an SGLT-2 inhibitor [11]. Semaglutide was also evaluated for its efficacy when added to the background treatment of basal insulin, which is known to cause weight gain [6, 18], especially at higher doses [26]. During SUSTAIN 5, patients taking basal insulin also exhibited clinically significant weight loss of at least 5% [9]. Patients with type 2 diabetes are frequently on multiple antihyperglycemic agents, especially when hyperglycemia is uncontrolled; thus, these findings of the addition of semaglutide to a pre-existing regimen are encouraging.

The SUSTAIN clinical trial program demonstrated that semaglutide has a similar safety profile to other agents within its drug class (Table 2). The most commonly recorded adverse events throughout each trial were GI events, typically nausea and vomiting, and primarily mild to moderate in severity [6, 8-16]. This is similar across all GLP-1 RAs currently on the market [19]. Also identical is the cardiovascular risk factor profile of semaglutide. SUSTAIN 6 outlined the cardiovascular outcomes of patients with a history of cardiovascular disease taking 0.5 mg or 1.0 mg semaglutide compared with a placebo-control group and found that patients taking semaglutide were less likely to suffer from nonfatal myocardial infarctions, nonfatal stroke, and cardiovascular death [8]. Increased pancreatic lipase was found in 4%–10% of patients throughout all trials comprising the SUSTAIN program [10, 12, 13]. The use of semaglutide is contraindicated in patients with a history of idiopathic acute or chronic pancreatitis [10]. There were very few cases of severe hypoglycemia, characteristic of GLP-1 RAs [6, 8-16].

There are limitations to the duration, generalizability, and design of the trials. The shortness of the trials' duration was noted in SUSTAIN 1, 2, 4, 5, 7, 8, 9, and 10 [6, 9, 10, 11, 13-16]. The chronic nature of type 2 diabetes makes many comorbid risk factors more likely as the disease progresses. Low generalizability was cited in SUSTAIN 1, 2, 4, 6, 7, 8, and 9. [6, 10, 11, 13, 15, 16]. Most of these issues with generalizability encompass the trial's ability to be applied to a regular clinical patient population, considering each trial's numerous exclusion factors. Design-related limitations vary between studies. SUSTAIN 2, 3, 4, 7, and 10 cited open-label designs [6, 12, 14, 16] or the inability to masque the identity of the trial products due

to their route of administration [13]. Others found difficulty with enforcing titration of basal insulins when used [6, 9, 12]. SUSTAIN 1 cited frequent use of rescue medication in its population as a limitation [10]. SUSTAIN 2 noted limited participants on background thiazolidinediones [13]. SUSTAIN 10 conceded their exclusion of using the 0.5 mg dose of semaglutide and 1.8 mg dose of liraglutide was also a limitation [14].

The present review is not without limitations either. This literature review excluded trial data from SUSTAIN CHINA MRCT, SUSTAIN (Japan), and SUSTAIN (Japan, sitagliptin). Further, to keep this review brief and concise, we included the most relevant endpoints for those seeking to look into using semaglutide at a clinical level—HA1c reduction, weight reduction, and safety outcomes, primarily. For further reading on these trials' full results, it is advised that the reader consult the trials themselves. Other essential summaries of the contents of the SUSTAIN program have been published [27-30].

5. Conclusions

The SUSTAIN clinical trial program found semaglutide suitable for FDA approval due to its effects of lowering glycated hemoglobin, cardiovascular risk and body weight. While these trials demonstrated these crucial findings, future investigations should consider longer duration trials and trials investigating the cardiovascular risks of concomitant use of semaglutide with other antidiabetic medications.

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Declaration of Competing Interest

The authors declare that there are no competing financial interests.

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