Diabetes & Metabolism 45 (2019) 409–418

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Review

Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1–7 trials

V.R. Aroda [a,*], A. Ahmann [b], B. Cariou [c], F. Chow [d], M.J. Davies [e], E. Jódar [f], R. Mehta [g], V. Woo [h], I. Lingvay [i]

[a] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b] Harold Schnitzer Diabetes Health Center at Oregon Health and Science University, Portland, OR, USA
[c] L'institut du thorax, CHU de Nantes, CIC 1413, Inserm, Nantes, France
[d] Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong
[e] Diabetes Research Centre, University of Leicester, Leicester, UK
[f] Hospital Universitario Quirón Salud Madrid, Facultad de Ciencias de la Salud, Universidad Europea de Madrid, Madrid, Spain
[g] Unidad de Investigacón en Enfermedades Metabolicas, Departamento de Endocrinologia y Metablismo, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" Mexico City, Mexico
[h] Section of Endocrinology and Metabolism, Health Sciences Centre, University of Manitoba, Winnipeg, MB, Canada
[i] UT Southwestern Medical Center, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 27 September 2018
Received in revised form 6 December 2018
Accepted 16 December 2018
Available online 4 January 2019

Keywords:
Cardiovascular
Efficacy
Glucagon-like peptide-1 receptor agonist
Semaglutide, SUSTAIN
Type 2 diabetes

ABSTRACT

In individuals with type 2 diabetes, glycaemic control and cardiovascular risk factor management reduces the likelihood of late-stage diabetic complications. Guidelines recommend treatment goals targeting HbA_{1c}, body weight, blood pressure, and low-density lipoprotein cholesterol. Development of new treatments for type 2 diabetes requires an understanding of their mechanism and efficacy, as well as their relative effects compared to other treatment choices, plus demonstration of cardiovascular safety. Subcutaneous semaglutide is a glucagon-like peptide-1 receptor agonist currently approved in several countries for once-weekly treatment of type 2 diabetes. Semaglutide works via the incretin pathway, stimulating insulin and inhibiting glucagon secretion from the pancreatic islets, leading to lower blood glucose levels. Semaglutide also decreases energy intake by reducing appetite and food cravings, and lowering relative preference for fatty, energy-dense foods. Semaglutide was evaluated in the SUSTAIN clinical trial programme in over 8000 patients across the spectrum of type 2 diabetes. This review details the efficacy and safety profile of semaglutide in the SUSTAIN 1–5 and 7 trials, and its cardiovascular safety profile in the SUSTAIN 6 trial. Semaglutide consistently demonstrated superior and sustained glycemic control and weight loss vs. all comparators evaluated. In SUSTAIN 6, involving patients at high risk of cardiovascular disease, semaglutide significantly decreased the occurrence of cardiovascular events compared with placebo/standard of care (hazard ratio 0.74, $P < 0.001$ for non-inferiority). Through a comprehensive phase 3 clinical trial program, we have a detailed understanding of semaglutide's efficacy, safety, cardiovascular effects and comparative role in the treatment of type 2 diabetes.

Introduction

In individuals with type 2 diabetes (T2D), adequate glycaemic control and cardiovascular (CV) risk factor management reduces the likelihood of late-stage diabetic micro- and macrovascular complications [1].

However, despite efforts with lifestyle intervention, most patients still require additional pharmacological therapy to achieve and maintain glycaemic control [1]. Although there are numerous pharmacological therapies available for the treatment of

* Corresponding author at: Diabetes Clinical Research, Brigham and Women's Hospital, Harvard Medical School, 221, Longwood Avenue, Boston, 02115 MA, USA.
E-mail addresses: varoda@bwh.harvard.edu (V.R. Aroda), ahmanna@ohsu.edu (A. Ahmann), bertrand.cariou@univ-nantes.fr (B. Cariou), b410773@mailserv.cuhk.edu.hk (F. Chow), melanie.davies@uhl-tr.nhs.uk (M.J. Davies), esteban.jodar@gmail.com (E. Jódar), roopamehta@yahoo.com (R. Mehta), vwoo3@shaw.ca (V. Woo), Ildiko.Lingvay@UTSouthwestern.edu (I. Lingvay).

https://doi.org/10.1016/j.diabet.2018.12.001
1262-3636/

T2D, it is estimated that a third to nearly a half of patients still fail to meet their targets for glycaemic control, blood pressure, and low-density lipoprotein cholesterol (LDL-C) levels [2]. Furthermore, there is a need for treatments that maximize efficacy, adherence and improvement in CV risk as well as quality of life [3].

The vast majority (~86%) of patients with T2D are overweight or obese [4]. In such patients, modest (≥ 5% of body weight) and sustained weight loss has been shown to improve glycaemic control and reduce the need for glucose-lowering medications [5,6].

Diabetes significantly increases the risk of atherosclerotic CV disease [7,8]. Since 2008, a number of CV outcomes trials have completed, evaluating the safety profile of new treatments for T2D [9–20]. Differential effects of treatments on glycaemia, weight, hypertension and dyslipidaemia may further influence CV risk [8,21,22]. The recent joint American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) Consensus Report highlights the importance of considering CV disease history early in the diabetes treatment pathway. This is based on the evidence that several sodium–glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve CV outcomes and progression of renal impairment in patients with T2D at high CV risk [23].

Semaglutide has 94% amino acid sequence homology with native human GLP-1, with several modifications that enable increased binding of albumin and slowed degradation in plasma [24]. Subcutaneous semaglutide is a GLP-1RA currently approved by the US Food and Drug Administration (FDA) [25], European Medicines Agency [26], Health Canada [27], and Japan's Ministry of Health, Labour and Welfare [28] for the once-weekly treatment of T2D. The phase 3 programme (PIONEER) for an oral form of semaglutide is underway with full results from PIONEER 1–6 expected in 2019.

Semaglutide works via the incretin pathway, which stimulates insulin and inhibits glucagon secretion from the pancreatic islets in a glucose-dependent manner, leading to lower blood glucose levels with low risk for hypoglycaemia [29]. Treatment with semaglutide results in weight loss, the mechanism of which is not fully understood, although studies in animal models have shown that liraglutide, another GLP-1RA, can access the central nervous system and likely mediates weight loss through its action on pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript-expressing arcuate nucleus neurons [30]. Clinically, semaglutide has been shown to lower energy intake by reducing appetite and food cravings, improve control of eating and meal portion size management, and lower relative preference for fatty, energy-dense foods [31].

The SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial programme included seven randomized controlled phase 3 trials involving more than 8000 patients with T2D [14,32–37]. Six efficacy trials, SUSTAIN 1–5 and SUSTAIN 7, were designed to evaluate the efficacy and safety of semaglutide vs. comparators, and covered a broad range of the T2D treatment continuum [32–37]. SUSTAIN 6 was a safety trial designed to evaluate CV and other long-term outcomes with semaglutide in patients with T2D who were at high CV risk [14]. Here, we provide an overview of the efficacy and safety profile of semaglutide in the SUSTAIN 1–5 and 7 clinical trials, as well as its CV safety profile in the SUSTAIN 6 trial.

Overview of the SUSTAIN 1–7 trials

The designs and patient baseline characteristics of the SUSTAIN 1–7 trials have been published previously, and are summarized in Table S1 and S2 (see supplementary materials associated with this article on line) [14,32–37]. In brief, the six efficacy trials were randomized, parallel-group, multicentre, controlled trials representing a broad range of the continuum of T2D care (Table S1 and S2 (see supplementary materials associated with this article on line) [32–37]. SUSTAIN 1, 2 and 5 were double-blinded trials, while SUSTAIN 3, 4, and 7 were open-label. Comparators were placebo (SUSTAIN 1, 5 and 6), sitagliptin (SUSTAIN 2), exenatide extended release (ER) (SUSTAIN 3), insulin glargine (IGlar) (SUSTAIN 4), and dulaglutide (SUSTAIN 7). Two doses of subcutaneous semaglutide were evaluated (0.5 mg and 1.0 mg), except in SUSTAIN 3 where only semaglutide 1.0 mg was evaluated. All semaglutide-treated patients followed a fixed dose-escalation regimen from a starting dose of semaglutide 0.25 mg, with dose doubling every 4 weeks until the trial dose was achieved.

Primary endpoints for SUSTAIN 1–5 and 7 were changes in HbA_{1c} from baseline to the end of treatment [32–37]. Secondary endpoints included changes from baseline in fasting plasma glucose (FPG), mean self-measured blood glucose (SMBG) and SMBG increment [32–37].

Efficacy analyses for SUSTAIN 1–5 and 7 were based on all randomized and exposed patients using on-treatment data collected prior to onset of rescue medication [32–37]. Safety analyses for SUSTAIN 1–5 and 7 were based on all randomized patients who had received ≥ 1 dose of randomized semaglutide s.c. or placebo [32–37]. Standard safety reporting was performed for all adverse events (AEs). Severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia was defined as an episode that is severe according to the ADA classification [38] or BG-confirmed by a plasma glucose value < 3.1 mmol/L (56 mg/dL; 1 mmol/L = 18.02 mg/dL), with symptoms consistent with hypoglycaemia.

SUSTAIN 6 was a multicentre, double-blinded CV outcomes trial in which semaglutide 0.5 mg and 1.0 mg doses were compared with placebo (Table S1; see supplementary materials associated with this article on line) [14]. To date, SUSTAIN 6 is the longest trial with semaglutide, lasting 104 weeks [14]. The primary endpoint was time to first occurrence of a major adverse CV event (MACE), defined as death from CV causes, non-fatal myocardial infarction or non-fatal stroke. In SUSTAIN 6, the primary hypothesis was non-inferiority, compared with placebo. This was confirmed if the upper boundary of the two-sided 95% confidence interval of the hazard ratio was below the non-inferiority margin of 1.8, in line with FDA guidance on the evaluation of CV risk in new therapies for T2D [39]. Testing for superiority for the primary outcome was not pre-specified and there was no adjustment for multiplicity.

Clinical evidence

Baseline characteristics and patient disposition across the SUSTAIN 1–7 trials are summarized in Table S2 (see supplementary materials associated with this article on line) [14,32–37,40,41]. A total of 8416 patients with T2D were randomized to once-weekly subcutaneous semaglutide 0.5 mg or 1.0 mg or comparators [14,32–37]. Over 90% of patients completed each trial [14,32–37].

Glycaemic control

Changes in HbA_{1c} from baseline to the end of the trial in all the SUSTAIN trials are summarized in Table 1 and Fig. 1a [14,32–37]. Across SUSTAIN 1–5 and 7, mean HbA_{1c} decreased from baseline (range 8.1–8.4%) by 1.2–1.5% with semaglutide 0.5 mg and 1.5–1.8% with semaglutide 1.0 mg, vs. < 0.1–0.4% with placebo and 0.5–1.4% with full doses of active comparators including sitagliptin, exenatide ER, IGlar (treated to target defined as pre-breakfast SMBG of 4.0 to 5.5 mmol/L (72 to 99 mg/dL), with no maximum insulin dose

Table 1
Change from baseline in HbA_{1c}, body weight, blood pressure, and lipid parameters across SUSTAIN 1–7 and proportion of patients achieving targets.

	SUSTAIN 1 monotherapy 30 weeks			SUSTAIN 2 vs. sitagliptin 56 weeks			SUSTAIN 3 vs. exenatide ER 56 weeks		SUSTAIN 4 vs. IGlar 30 weeks			SUSTAIN 5 add-on to basal insulin 30 weeks			SUSTAIN 7 vs. dulaglutide 40 weeks				SUSTAIN 6 vs. placebo 104 weeks			
	Sema 0.5 mg	Sema 1.0 mg	PBO	Sema 0.5 mg	Sema 1.0 mg	Sita 100 mg	Sema 1.0 mg	Exe 2.0 mg	Sema 0.5 mg	Sema 1.0 mg	IGlar	Sema 0.5 mg	Sema 1.0 mg	PBO	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Sema 1.0 mg	PBO 0.5 mg	PBO 1.0 mg
Change from baseline																						
HbA_{1c} (%)	−1.5[a]	−1.6[a]	< −0.1	−1.3[a]	−1.6[a]	−0.5	−1.5[a]	−0.9	−1.2[a]	−1.6[a]	-0.8	-1.4[a]	-1.8[a]	-0.1	-1.5[a]	-1.1	-1.8[a]	-1.4	-1.1[a]	-1.4[a]	-0.4	-0.4
Body weight (kg)	−3.7[a]	−4.5[a]	−1.0	−4.3[a]	−6.1[a]	−1.9	−5.6[a]	−1.9	−3.5[a]	−5.2[a]	1.2	-3.7[a]	-6.4[a]	-1.4	-4.6[a]	-2.3	-6.5[a]	-3.0	-3.6[a]	-4.9[a]	-0.7	-0.5
SBP (mmHg)	−2.6	−2.7	−1.7	−5.1[a]	−5.6[a]	−2.3	−4.6[a]	−2.2	−4.7[a]	−5.2[a]	-1.7	-4.3	-7.3[a]	-1.0	-2.4	-2.2	-4.9	-2.9	-3.4	-5.4[a]	-2.2	-2.8
DBP (mmHg)	−0.5	0.2	0.4	−2.0	−1.9	−1.1	−1.0	−0.1	−1.4	−1.0	-1.4	-1.8	-1.5	-2.2	-0.6	-0.3	-2.0[a]	< -0.1	-1.4	-1.6	-1.4	-1.7
Pulse (bpm)	2.3	2.4	−0.5	1.6	1.8	0.6	2.1	1.1	2.3	3.1	< -0.1	0.8	4.0	-0.8	2.1	1.6	4.0	2.4	2.1	2.4	0.1	-0.1
ETR (semaglutide vs. comparator)																						
Total cholesterol	0.97	0.92[a]		0.98	0.98		0.98		0.96[a]	0.96[a]		0.95[a]	0.97		0.96		0.97		0.97[a]	0.99		
Triglycerides	0.93	0.92		0.98	0.92[a]		0.87[a]		0.96	0.94[a]		0.92	0.90[a]		0.91		0.86		0.97	0.93[a]		
HDL	1.01	0.97		1.00	1.04[a]		1.02		1.00	1.02[a]		0.99	1.01		0.99		1.01		1.00	1.04[a]		
LDL	0.99	0.92[a]		0.96	0.97		0.99		0.94[a]	0.93[a]		0.93	0.98		0.97		1.00		0.96[a]	0.99		
Proportion of patients achieving HbA_{1c} target, composite endpoint and weight-loss responses (%)																						
$HbA_{1c} < 7.0\%$	74%	72%	25%	69%	78%	36%	67%	40%	57%	73%	38%	61%	79%	11%	68%	52%	79%	67%	NR	NR	NR	NR
Composite endpoint ($HbA_{1c} < 7.0\%$, no weight gain, no severe or BG-confirmed hypoglycaemia)	66%	65%	19%	63%	74%	27%	56%	28%	47%	64%	16%	54%	67%	7%	64%	44%	74%	58%	NR	NR	NR	NR
Body weight ≥ 5%	37%	45%	7%	46%	62%	18%	52%	17%	37%	51%	5%	42%	66%	11%	44%	23%	63%	30%	NR	NR	NR	NR
Body weight ≥ 10%	8%	13%	2%	13%	24%	3%	21%	4%	8%	16%	2%	9%	26%	3%	14%	3%	27%	8%	NR	NR	NR	NR

BG: blood glucose; DBP: diastolic blood pressure; Dula: dulaglutide; ETR: estimated treatment ratio vs. (dose-matched) comparators (SUSTAIN 7: semaglutide 0.5 mg vs. dulaglutide 0.75 mg and semaglutide 1.0 mg vs. dulaglutide 1.5 mg); Exe: exenatide extended release; HDL: high-density lipoprotein cholesterol; IGlar: insulin glargine; LDL: low-density lipoprotein cholesterol; NR: not reported; PBO: placebo; SBP: systolic blood pressure; Sema: semaglutide; Sita: sitagliptin.

[a] $P < 0.05$ vs. (dose-matched) comparator (SUSTAIN 7: semaglutide 0.5 mg vs. dulaglutide 0.75 mg and semaglutide 1.0 mg vs. dulaglutide 1.5 mg).

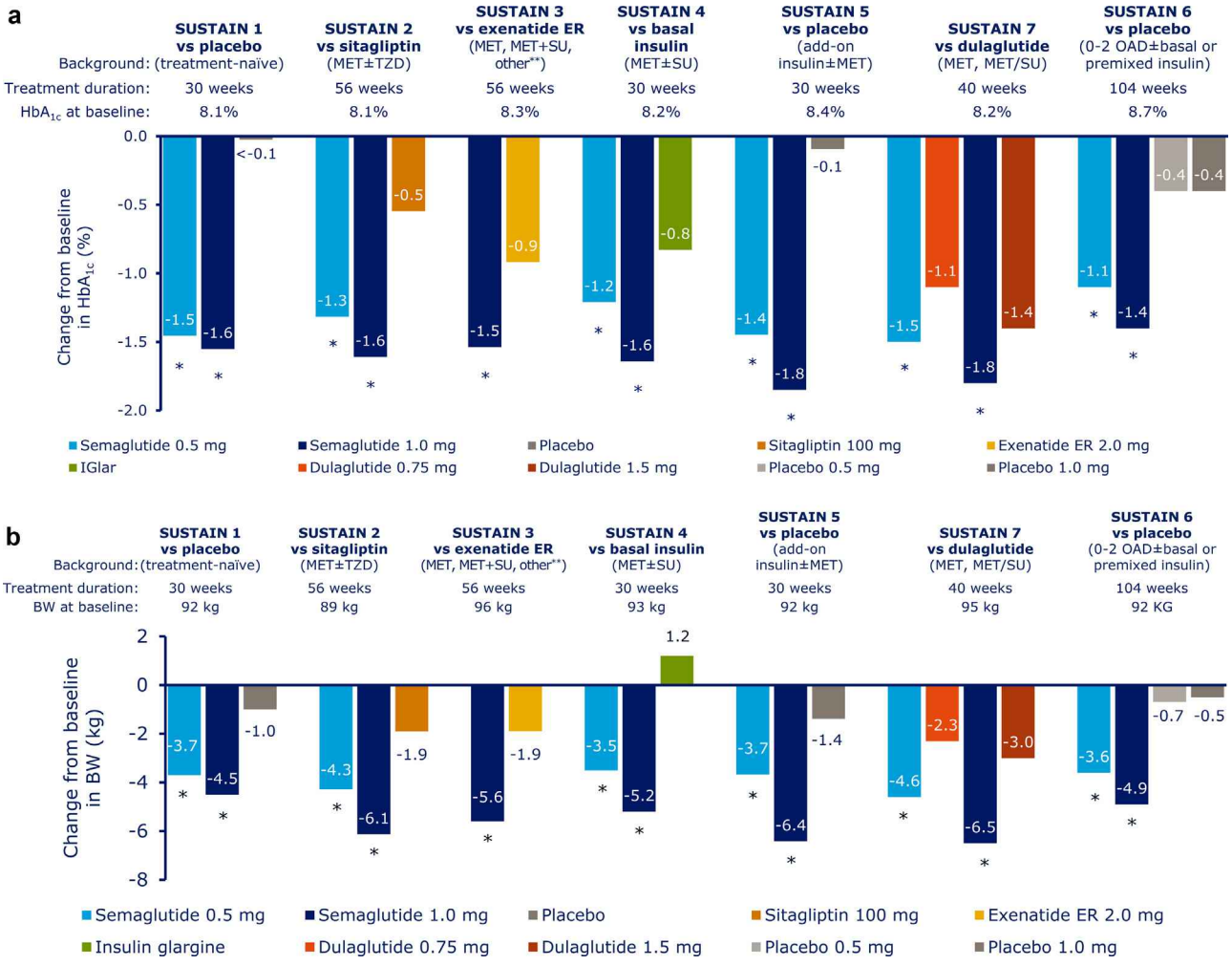

Fig. 1. Effect of semaglutide vs. comparators in SUSTAIN 1–7 on mean change from baseline in HbA_{1c} (a) and body weight (b). $^{*}P < 0.0001$ vs. comparator. BW: body weight; exenatide ER: exenatide extended release; IGlar: insulin glargine; MET: metformin; OAD: oral antidiabetic drug; SU: sulphonylurea; TZD: thiazolidinedione.

specified) and dulaglutide (Table 1 and Fig. 1a, all $P < 0.0001$ vs. comparators) [32–37]. In SUSTAIN 6, where adjustment of background medications was permitted in all groups, there was still a significant reduction in HbA_{1c} with semaglutide 0.5 mg and 1.0 mg vs. placebo (−1.1% vs. −0.4% and −1.4% vs. 0.4%, respectively) at week 104 (Table 1 and Fig. 1a) [14]. Additional analyses of a composite endpoint showed that across SUSTAIN 1–5 and 7, significantly more patients achieved $HbA_{1c} < 7.0\%$ with no weight gain and no severe or BG-confirmed symptomatic hypoglycaemia when treated with semaglutide 0.5 mg (47–66%) and semaglutide 1.0 mg (56–74%) once-weekly vs. comparators (7% and 19% with placebo, and 16–58% with active comparators) (all $P \leq 0.0001$) (Fig. 2) [32–37,42]. Results for mean FPG, mean SMBG and SMBG increment are shown in Table S3; see supplementary materials associated with this article on line.

Body weight and waist circumference

Across the SUSTAIN trials, semaglutide consistently demonstrated significantly greater body weight reductions from baseline to end of treatment vs. all comparators (Table 1 and Fig. 1b, all $P < 0.0001$) [14,32–37]. In SUSTAIN 1–5 and 7 (baseline range 89 to 95 kg), mean body weight decreased by 3.5–4.6 kg with semaglutide 0.5 mg and 4.5–6.5 kg with semaglutide 1.0 mg, vs. a weight reduction of 1.0–1.4 kg with placebo, and 3.0 kg with dulaglutide (SUSTAIN 7) or 1.9 kg with sitagliptin and exenatide ER (SUSTAIN 2 and 3), to a 1.2 kg weight increase with basal insulin (SUSTAIN 4) (Table 1 and Fig. 1b, all $P < 0.0001$ vs. comparators) [32–37]. In SUSTAIN 6, there was also a significant reduction in body weight, from a baseline of 92 kg, of 3.6 kg with semaglutide 0.5 mg and 4.9 kg with semaglutide 1.0 mg vs. 0.5 kg and 0.7 kg with placebo at Week 104 ($P < 0.0001$) (Table 1 and Fig. 1b) [14]. The proportion of patients achieving $\geq 5\%$ or $\geq 10\%$ weight loss was significantly higher in patients treated with semaglutide vs. comparators. For example, the proportion of patients achieving $\geq 5\%$ weight loss across SUSTAIN 1–5 and 7 was 37–46% with 0.5 mg semaglutide and 45–66% with semaglutide 1.0 mg, compared with 7–11% with placebo and 5–30% with active comparators ($P < 0.0001$ for all pairwise comparisons between semaglutide 0.5 mg and 1.0 mg vs. comparators, Table 1) [32–37].

Across SUSTAIN 1–5 and 7 trials, semaglutide reduced mean waist circumference from baseline to end of treatment by 3.2–4.3 cm with semaglutide 0.5 mg (SUSTAIN 1, 2, 4, 5 and 7), 4.1–6.0 cm with semaglutide 1.0 mg (SUSTAIN 1–5 and 7), vs. 1.9–2.0 cm with placebo (SUSTAIN 1 and 5), and 2.9 cm with dulaglutide 1.5 mg (SUSTAIN 7) to an increase of 0.2 cm with IGlar (SUSTAIN 4) [32–37].

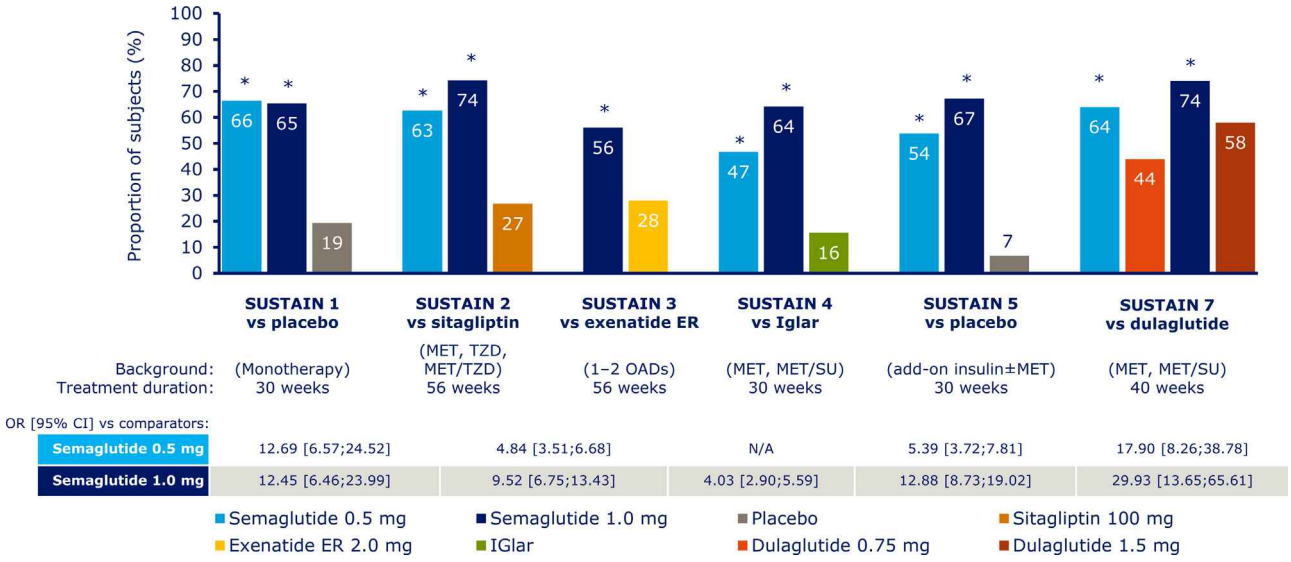

Fig. 2. Patients achieving $HbA_{1c} < 7.0\%$ with no weight gain and no severe or blood glucose-confirmed symptomatic hypoglycaemia. $^{*}P < 0.0001$ vs. comparator. CI: confidence interval; exenatide ER: exenatide extended release; IGlar: insulin glargine; MET: metformin; N/A: not applicable; OAD: oral antidiabetic drug; OR: odds ratio; SU: sulphonylurea; TZD: thiazolidinedione.

Combined effect on HbA_{1c} and body weight

In a secondary analysis of SUSTAIN 1–5, more patients treated with semaglutide achieved reductions in both HbA_{1c} and body weight vs. comparators [32–36,43]. Across the SUSTAIN trials, between 78% (SUSTAIN 1) and 93% (SUSTAIN 5) of patients receiving 1.0 mg semaglutide showed a reduction in both HbA_{1c} and body weight, while ≤ 2% of patients had no reduction in either. A scatter plot of the individual changes from baseline in HbA_{1c} (%) and body weight (%) at end of treatment across SUSTAIN 1–5 is shown in Fig. 3 [32–36,43].

Blood pressure, pulse and lipid parameters

Across SUSTAIN 1–5 and 7, treatment with semaglutide 0.5 mg and 1.0 mg resulted in similar or significantly greater reductions in systolic blood pressure vs. placebo and active comparators (Table 1) [32–37]. Changes from baseline in diastolic blood pressure were similar between semaglutide 0.5 mg, 1.0 mg, and comparators (Table 1). Treatment with semaglutide 0.5 mg and 1.0 mg led to an increase in pulse rate of between 0.8 bpm and 4.0 bpm vs. changes of −0.8 bpm to 2.4 bpm with placebo and active comparators.

Across SUSTAIN 1–5 and 7, treatment with semaglutide 0.5 mg and 1.0 mg also resulted in similar or significantly improved total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels vs. placebo and active comparators (Table 1) [32–37].

CV endpoints

In SUSTAIN 6, the primary outcome of CV death, non-fatal or non-fatal stroke occurred in 108 of 1648 patients in the semaglutide group vs. 146 of 1659 patients in the placebo group (hazard ratio 0.74; 95% confidence interval 0.58–0.95; $P < 0.001$ for non-inferiority). The trial was not powered to show superiority [14]. Analysis of the three components of the MACE composite endpoint showed that semaglutide significantly reduced the risk of non-fatal stroke vs. placebo, but not non-fatal MI and CV death [14].

Safety profile

The overall incidences of serious AEs across the SUSTAIN 1–5 and 7 trials were similar between semaglutide arms vs. comparators (Table S4; see supplementary materials associated with this article on line) [32–37]. The proportion of patients reporting an AE was similar or higher than comparators, primarily as a result of greater prevalence of GI disorders. The proportion of patients reporting GI disorders ranged from 27% to 44% with semaglutide and 15% (placebo) to 48% (1.5 mg dulaglutide) with comparators (Table S4; see supplementary materials associated with this article on line; Fig. 4) [32–37,44]. GI disorders, notably nausea, vomiting and diarrhoea, were the most common AEs reported by patients receiving semaglutide (Table S4; see supplementary materials associated with this article on line) [32–37]. Most nausea events were generally mild to moderate in severity, and improved over time for most patients [32–37]. In SUSTAIN 6, similar proportions of patients experienced AEs and serious AEs in all four treatment groups (semaglutide 0.5 mg, semaglutide 1.0 mg, placebo 0.5 mg and placebo 1.0 mg) [14]. Incidences of malignant neoplasms, cholelithiasis, elevated lipase and pancreatitis in SUSTAIN 6 are summarized in Table S4; see supplementary materials associated with this article online.

Across SUSTAIN 1–5 and 7, the reporting of diabetic retinopathy AEs were comparable across treatments and all events were mild to moderate – there were no serious AEs. These trials excluded patients with pre-existing proliferative retinopathy and maculopathy requiring acute treatment [32–37]. However, in SUSTAIN 6, in which there were no exclusion criteria related to diabetic retinopathy and therefore a higher number of patients had diabetic retinopathy at baseline vs. other SUSTAIN trials, a greater proportion of diabetic retinopathy AEs was reported in patients receiving semaglutide vs. placebo (Table S4; see supplementary materials associated with this article on line) [14]. This may be linked to semaglutide treatment in SUSTAIN 6 resulting in a more rapid and pronounced reduction in HbA_{1c} vs. placebo [45].

Across SUSTAIN 1–7, the proportion of patients who experienced an AE leading to premature treatment discontinuation was higher in those who received semaglutide vs. comparators (5–14% vs. 1–8% with placebo in SUSTAIN 1, 5 and 6, and 1–7% with active comparators in SUSTAIN 2, 3, 4 and 7, Table S4 (see supplementary materials associated with this article online) [14,32–37].

The proportions of subjects who experienced severe or BG-confirmed symptomatic hypoglycaemia across SUSTAIN 1–7 were generally similar or lower with semaglutide vs. comparators (Fig. 5) [14,32–37]. In SUSTAIN 4, more patients receiving

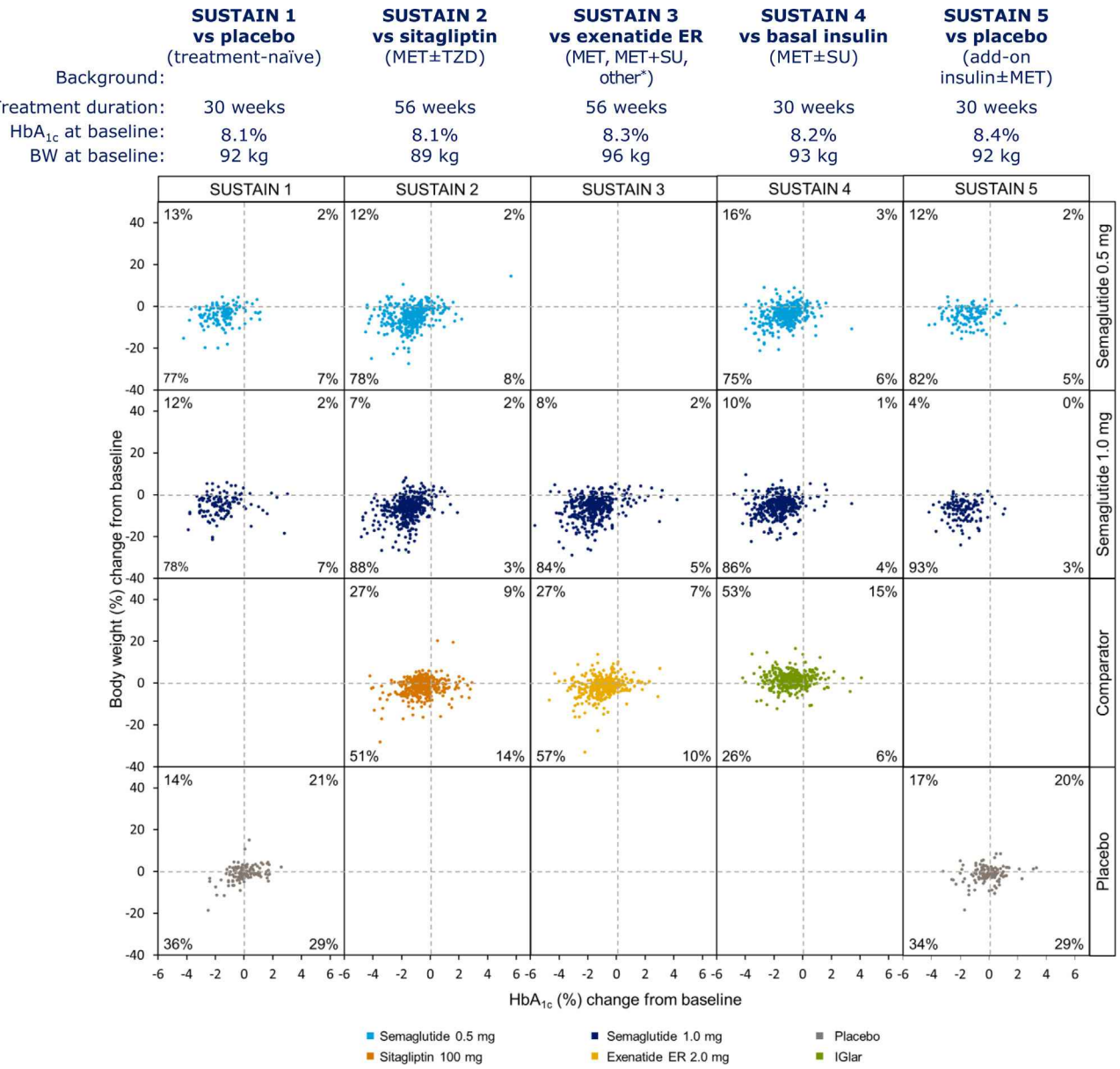

Fig. 3. Scatter plot of individual change from baseline in HbA_{1c} (%) and body weight (%) at end of treatment in SUSTAIN 1–5. The four percentage values shown for each quadrant of the individual scatter plots indicate the corresponding respective proportions of the total subjects within each treatment group. For some quadrants, percentage values do not sum to 100% due to rounding. BW: body weight; exenatide ER: exenatide extended release; IGlar: insulin glargine; MET: metformin; SU: sulphonylurea; TZD: thiazolidinedione.

sulphonylureas at baseline experienced hypoglycaemia vs. those who did not receive sulphonylureas at baseline (Fig. 5) [35]. This was also the case in SUSTAIN 3, in which the majority of hypoglycaemia events were reported in subjects concomitantly receiving sulfonylureas in both the semaglutide and exenatide ER groups [34].

In SUSTAIN 5, in which only patients treated with insulin were enrolled, those with baseline $HbA_{1c} \leq 8.0\%$ at screening had a higher rate of severe or BG-confirmed hypoglycaemia with semaglutide compared with placebo, although the proportion of patients in this category who experienced any hypoglycaemia was similar to those with $HbA_{1c} > 8.0\%$ at screening [36].

SUSTAIN 2, 3 and 6 are the only SUSTAIN trials with published data on anti-semaglutide antibodies to date [14,33,34]. In SUSTAIN 2, six semaglutide-treated subjects developed anti-semaglutide antibodies, which crossed-reacted with endogenous GLP-1 in three participants [33]. These antibodies did not have an in-vitro neutralizing effect on semaglutide or endogenous GLP-1 in any subjects [33]. In SUSTAIN 3, anti-semaglutide antibodies developed in 13 subjects; none were neutralizing to semaglutide or endogenous GLP-1 [34]. In SUSTAIN 6, antibodies against semaglutide were detected in 30 patients treated with semaglutide [14]. In the majority of subjects, antibody formation was transient and only four subjects tested positive during follow-up [14].

In trials where injection-site reaction data were published, events with semaglutide ranged from 0 to 2% in SUSTAIN 3, 6 and 7, vs. 12% for exenatide ER (SUSTAIN 3), 1–2% for placebo (SUSTAIN 6) and 1–3% for dulaglutide (SUSTAIN 7) [14,34,37].

Patient-reported outcomes were assessed in all trials, with a limitation in interpretation being the open-label design of SUSTAIN 3, 4 and 7. However, these outcomes were assessed in a double-blinded manner in SUSTAIN 2. In this trial, improvements in overall diabetes treatment satisfaction, as measured by the Diabetes Treatment Satisfaction Questionnaire were significantly greater for

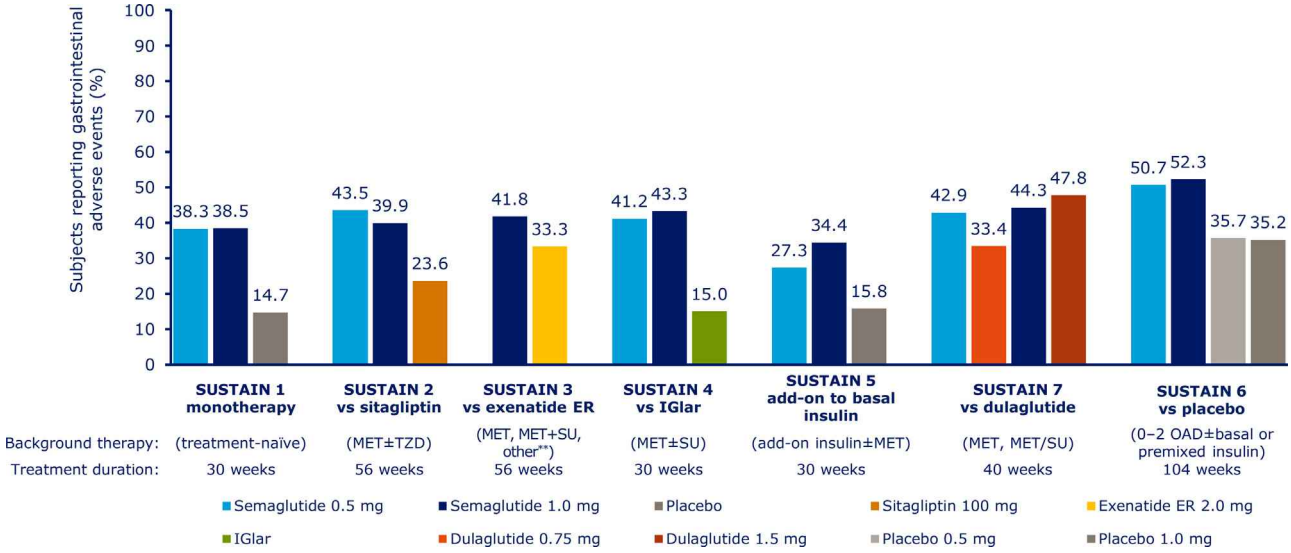

Fig. 4. Gastrointestinal disorders in SUSTAIN 1–7. Exenatide ER: exenatide extended release; IGlar: insulin glargine; MET: metformin; OAD: oral antidiabetes drug; SU: sulphonylurea; TZD: thiazolidinedione.

semaglutide vs. sitagliptin (SUSTAIN 2) ($P < 0.05$); the same was true for self-perceived hyperglycaemia (i.e., where the participant felt that their blood sugars had been unacceptably high; $P < 0.05$) with similar observations in the open-label SUSTAIN 3 (vs. exenatide ER; $P < 0.05$) and 4 (vs. IGlar; $P < 0.03$) trials [33–35,37]. Overall, patients in SUSTAIN 2 were significantly more satisfied with semaglutide as their current treatment vs. sitagliptin ($P < 0.05$) and vs. exenatide ER and IGlar in SUSTAIN 3 and 4 ($P < 0.05$ and $P < 0.03$, respectively) [33–35]. Significantly more patients in SUSTAIN 2 and 3 would recommend semaglutide to others with T2D [33,34] while significantly more patients in SUSTAIN 3 were satisfied to continue treatment with semaglutide over exenatide ER [34]. In the open-label SUSTAIN 7 trial, semaglutide 0.5 mg and 1.0 mg demonstrated improvements from baseline in patient-reported outcomes that were similar to those for dulaglutide 0.75 mg and 1.5 mg, respectively [37]. Patient perception of unacceptable hyperglycaemia was significantly improved with semaglutide 0.5 mg vs. dulaglutide 0.75 mg (estimated treatment difference [ETD] –0.32 [95% confidence interval –0.60;–0.04], $P = 0.0254$) and semaglutide 1.0 mg vs. dulaglutide 1.5 mg (ETD –0.40 [95% confidence interval –0.68;–0.12], $P = 0.0049$) [37].

Discussion

GLP-1RAs are considered efficacious agents for treating T2D with the added benefit of weight loss and a low risk for hypoglycaemia [1]. In the SUSTAIN 1–5 and 7 trials, semaglutide consistently reduced HbA_{1c}, improved FPG and SMBG profiles, and induced greater weight loss vs. comparators, with a lower risk of hypoglycaemia (excluding placebo and sitagliptin) in patients with T2D [32–37]. The SUSTAIN programme included head-to-head trials comparing semaglutide with current clinical choices for treatment intensification, with semaglutide demonstrating superior glycaemic control vs. a dipeptidyl peptidase-4 inhibitor

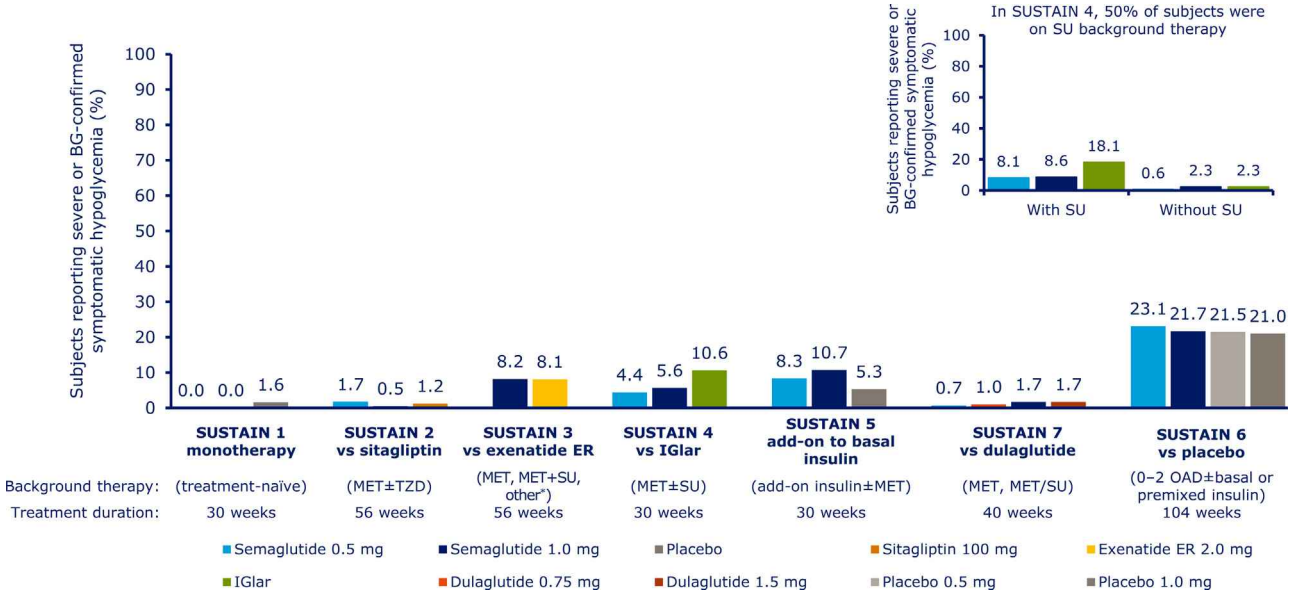

Fig. 5. Severe or blood glucose-confirmed symptomatic hypoglycaemia in SUSTAIN 1–7. BG: blood glucose; exenatide ER: exenatide extended release; IGlar: insulin glargine; MET: metformin; OAD: oral antidiabetic drug; SU: sulphonylurea; TZD: thiazolidinedione.

(sitagliptin), other once-weekly GLP-1RAs (exenatide ER and dulaglutide), and basal insulin (IGlar) [32–37].

As well as helping patients achieve glycaemic control, it is also important for novel treatments for T2D to demonstrate CV safety [1]. To date, an SGLT-2 inhibitor (empagliflozin) and a GLP-1RA (liraglutide once daily) are the only treatments approved for reducing the risk of CV disease for patients with T2D [1]. The use of agents with proven CV benefits from the SGLT-2 inhibitor and GLP-1RA classes in populations at high CV risk is also highlighted in the 2018 update of the ADA/EASD Consensus Report [23].

Overall, there are now seven CV outcomes trials of GLP-1RAs, three of which have demonstrated CV safety but not superiority (lixisenatide, ITCA 650, and exenatide ER) [15,16,46], and four that have demonstrated both CV safety and superiority (liraglutide, semaglutide, albiglutide, and dulaglutide), in terms of MACE reduction [13,14,18,19]. Of the SGLT-2 inhibitors, two have demonstrated CV safety and superiority [11,12], and one has demonstrated CV safety [20,47].

In SUSTAIN 6, semaglutide demonstrated CV safety vs. placebo [14] and, although not currently indicated [48–50], demonstrated significant reduction in CV events vs. placebo/standard-of-care [1]. In the EXSCEL trial, once-weekly exenatide ER demonstrated CV safety vs. placebo, but not superiority in regard to reducing the incidence of the three-component MACE outcome (hazard ratio 0.91; 95% confidence interval 0.83–1.00; $P = 0.06$) [19]. The once-weekly GLP-1RA albiglutide has demonstrated a significant reduction in MACE (hazard ratio 0.78; 95% confidence interval 0.68–0.90; $P = 0.0006$ for superiority) in patients with T2D and established CV disease in the Harmony Outcomes trial [18].

In the LEADER trial, the once-daily GLP-1RA liraglutide, showed a 13% reduction in the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke and a 22% reduction vs. placebo in death from CV causes with liraglutide vs. placebo [13]. However, SUSTAIN 6 had a shorter trial duration than LEADER (2.1 vs. 3.8 years) and involved fewer subjects (3,297 vs. 9,340) [13,14]. Hence, further studies with semaglutide may be required to provide additional information on outcomes such as CV death. In addition, the PIONEER 6 trial (NCT02692716) is investigating the CV safety of oral semaglutide in subjects with T2D; this trial completed in 2018 and results are expected in 2019.

These results suggest that semaglutide and liraglutide may share similar mechanisms for the reduction of CV risk by attenuating atherosclerotic progression, which differs from the effect of SGLT-2 inhibitors on CV death [11–14]. This may also be a general effect of the GLP-1RA class, although further research is required to confirm this hypothesis [51].

Another difference between the SGLT-2 inhibitor and GLP-1RA classes is with regards to heart failure (HF). Three SGLT-2 inhibitors have demonstrated a significant reduction in the risk of hospitalization for HF vs. placebo in CV outcomes trials: empagliflozin, canagliflozin, and dapagliflozin [11,12,20]. Furthermore, in patients with T2D and HF, the use of SGLT-2 inhibitors as second-line treatment is preferred [23]. In the LIVE study, which investigated patients with chronic HF with or without T2D, there was no direct effect of liraglutide on left ventricular systolic function and an increased risk of serious cardiac events was observed [52]. In CV outcomes trials of patients with T2D, the GLP-1RAs liraglutide, semaglutide and albiglutide have shown no significant effect on the risk of hospitalization for HF [13,14,18].

Finally, effects of GLP-1RAs on renal outcomes have also gained increasing attention. Both LEADER and SUSTAIN 6 demonstrated a significant reduction in renal outcomes with liraglutide and semaglutide, respectively, with a slower decline in estimated glomerular filtration rate (eGFR) seen with both liraglutide and semaglutide (post-hoc analysis of SUSTAIN 6), compared with placebo [13,14,53]. In addition, both have demonstrated safety in populations with eGFR $\geq$ 15 mL/min/1.73 m^2 [54]. Furthermore, lower proportions of subjects experienced new or worsening nephropathy with semaglutide vs. placebo [14], which may be suggestive of a potential renal protective effect. Current data supporting SGLT-2 inhibitor-mediated reductions in chronic kidney disease progression are compelling however, and the use of SGLT-2 inhibitors as second-line treatment is preferred in patients with T2D and chronic kidney disease [23].

In addition to the improvements in glycaemic control and in CV safety demonstrated with semaglutide treatment, the clinically meaningful reductions in body weight vs. comparators shown in the SUSTAIN 1–5 and 7 trials [32–37] are also key, given the benefits of weight loss on glycaemic control, insulin sensitivity and risk of CV disease [1]. The degree of weight loss achieved with semaglutide 0.5 mg and 1.0 mg was also numerically higher than that reported previously with other GLP-1RAs [55]. These data have been incorporated into treatment guidelines, which now advocate preferential use of semaglutide before other GLP-1RAs if there is a need to promote weight loss [23]. Comprehensively, the semaglutide phase 3 programme indicates that semaglutide is efficacious across different background treatments and stages in the treatment continuum [32–37]. Recently, a pooled analysis of the SUSTAIN trials demonstrated that semaglutide treatment had a comparable efficacy and safety profile in elderly ($\geq$ 65 years) patients with T2D vs. non-elderly ($<$ 65 years) patients [56].

Safety findings were generally consistent with known effects of GLP-1 RA. Fewer than 10% of patients discontinued treatment with semaglutide due to adverse events, reflecting an overall favourable safety and tolerability profile across the SUSTAIN 1–7 trials [14,32–37]. As expected for a therapy with a glucose-dependent mechanism of action, rates of hypoglycaemia were generally low. Severe or BG-confirmed symptomatic hypoglycaemia events were fewer or similar with semaglutide vs. comparators, irrespective of background OAD treatment, except when combined with sulphonylurea or insulin (SUSTAIN 3, 4 and 5) where higher rates of hypoglycaemia were observed [14,32–37]. In addition, the rates of pancreatitis-related events across SUSTAIN 1–7 were low and comparable between semaglutide, placebo, and active comparators [14,32–37].

In SUSTAIN 6, a greater proportion of patients randomized to semaglutide had diabetic retinopathy events vs. placebo [14]. However, rates of diabetic retinopathy were balanced between treatments across SUSTAIN 1–5 and 7 [32–37]. In SUSTAIN 6, a greater proportion of patients who experienced worsening diabetic retinopathy had diabetic retinopathy at baseline vs. the general trial population [14]. Similar findings have also been reported in the Diabetes Control and Complications Trial (DCCT) for patients with type 1 diabetes, and in the UK Prospective Diabetes Study (UKPDS 33) in newly diagnosed T2D patients; in these studies, rapid and marked reductions in HbA_{1c}, resulting in improved glycaemic control, were associated with transitory worsening of diabetic retinopathy [57,58]. A post-hoc mediation analysis suggested that the increase in diabetic retinopathy complications with semaglutide vs. placebo may be associated with the large and rapid decline in HbA_{1c} during the first 16 weeks of treatment. Furthermore, most patients with diabetic retinopathy complications had a longer diabetes disease duration, higher HbA_{1c} at baseline and had a history of insulin treatment compared with those who did not [45]. However, further evidence is required to fully understand the effect of semaglutide on diabetic retinopathy. In the meantime, physicians should be aware of the risk of worsening diabetic retinopathy in association with rapid and large glycaemic reductions, particularly in patients also receiving insulin [45]. All patients with a history of diabetic retinopathy should be closely monitored for progression of diabetic retinopathy when a rapid drop in HbA_{1c} is achieved [49].

While each trial was robust in terms of their respective sample sizes to power individual statistical analyses, disparities in trial designs such as varying treatment durations and baseline characteristics among patients across the SUSTAIN 1–7 trials limits any direct between-trial comparisons. Conversely, this is one of the largest analyses of patients treated with a GLP-1RA to date, involving more than 8000 patients.

Additional trials exploring the potential for semaglutide as an oral therapy for T2D (NCT02863328), and as a potential treatment for obesity (NCT02453711) are planned or ongoing. Also of interest will be the results of SUSTAIN 8, an ongoing phase 3b trial comparing semaglutide and the SGLT-2 inhibitor canagliflozin (NCT03136484) and SUSTAIN 9, comparing semaglutide versus placebo as an add-on to SGLT-2 inhibitor monotherapy or in combination with either metformin or sulfonylurea (NCT03086330).

Conclusion

In a comprehensive phase 3 clinical trial program with over 8000 participants, once-weekly semaglutide, a newly approved GLP-1RA, consistently demonstrated greater glycaemic efficacy combined with greater weight loss than comparator therapies, across a broad range of patients with T2D vs. all comparators evaluated. The safety profile of semaglutide was similar to that of other GLP-1RAs [59], and the CV safety of semaglutide is now well established. In the SUSTAIN 6 trial involving patients at high risk of CV disease, semaglutide lowered the risk of adverse CV outcomes compared with placebo added to standard of care. Forthcoming and ongoing studies include evaluation of oral semaglutide for T2D, of subcutaneous semaglutide for the treatment of obesity, and of subcutaneous semaglutide once weekly vs. an SGLT-2 inhibitor in a head-to-head trial. As the landscape of diabetes therapeutics continues to expand and evolve, it is important that new agents are evaluated in a way that will inform clinical practice, as has been done with semaglutide, offering an understanding of the comparative efficacy, safety, and CV effects of semaglutide in patients with T2D.

Funding

This work was funded by Novo Nordisk A/S, which also had a role in the review of the manuscript for scientific accuracy. Novo Nordisk A/S had no role in the planning or design of the manuscript; in the analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

Disclosure of interests

VRA has received consultancy fees from Adocia, AstraZeneca, BD, Janssen, Novo Nordisk, Sanofi and Zafgen, and research support from Amylin, AstraZeneca/BMS, Boehringer Ingelheim, Calibra Medical, Eisai Inc, Elcelyx, GI Dynamics, GSK, N-Gene, Novo Nordisk, Sanofi, Takeda and Theracos Inc. AA has received consulting fees from Novo Nordisk and Dexcom, research support from Novo Nordisk, Sanofi, Lexicon and Dexcom, and travel support from Novo Nordisk. BC has received consulting fees from Novo Nordisk, research support from Sanofi, Regeneron, Pfizer and Novo Nordisk, and honoraria from Amgen, AstraZeneca, Pierre Fabre, Janssen, Eli Lilly, MSD Merck & Co, Novo Nordisk, Sanofi and Takeda. FC has received fees for advisory board participation from AstraZeneca, Eli Lilly and Novo Nordisk, and research support from Boehringer Ingelheim, Novo Nordisk and Takeda. MJD has received fees for advisory board participation from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi-Aventis and Servier, consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis, fees for speaker's bureau participation from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Novo Nordisk, Sanofi-Aventis and Takeda Pharmaceuticals International Inc, and research support from Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi-Aventis. EJ has received fees for advisory board participation from Novo Nordisk, consulting fees from AstraZeneca, Janssen, Eli Lilly and Novo Nordisk, fees for speaker's bureau participation from AstraZeneca, Eli Lilly, MSD and Novo Nordisk, and research support from AstraZeneca, Eli Lilly, GSK, Janssen, Merck Sharp & Dohme and Novo Nordisk. RM has received fees for advisory board participation from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk and Stendahl, and fees for speakers' bureau participation from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. VW received fees for advisory board participation from AstraZenenca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi, fees for speaker's bureau participation from AstraZenenca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi, and research support from AstraZenenca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. IL has received consulting fees from AstraZeneca, Eli Lilly, Intarcia, MannKind, Novo Nordisk (paid to the University of Texas Southwestern Medical Center), Sanofi and TARGET Pharma, research support from GI Dynamics, Merck, Mylan, Pfizer, Novartis, and Novo Nordisk, and editorial/travel support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi.

Acknowledgments

We thank all the participants, investigators and trial-site staff who were involved in the conduct of the SUSTAIN 1–7 trials. We also thank Desirée Thielke, MD and Jakob Ferløv Schwensen, MD PhD (Novo Nordisk), for their medical accuracy review of the outline and final draft of the manuscript, and Haydn Liang, PhD and Jamil Bacha, PhD (AXON Communications), for medical writing and editorial assistance, who received compensation from Novo Nordisk.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2018.12.001.

References

[1] American Diabetes Association. Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41(Suppl 1):S1–35.
[2] Khunti K, Ceriello A, Cos X, De Block C. Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2018;137:137–48.
[3] Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/02/WC500243464.pdf; 2018 [accessed 31 May 2018].
[4] Menke A, Knowler WC, Cowie CC. Physical and metabolic characteristics of persons with diabetes and prediabetes. Chapter 9. In: Diabetes in America, 3rd ed. Cowie CC, et al. Eds. Bethesda: MD, National Institutes of Health; 2017: 9–14.
[5] Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet 2015;115:1447–63.
[6] Wing RR, Espeland MA, Clark JM, Hazuda HP, Knowler WC, Pownall HJ, et al. Association of Weight Loss Maintenance and Weight Regain on 4-Year Changes in CVD Risk Factors: the Action for Health in Diabetes (Look AHEAD) Clinical Trial. Diabetes Care 2016;39:1345–55.
[7] Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.
[8] Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006;368:29–36.
[9] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–26.
[10] Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–42.
[11] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[12] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[13] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.
[14] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.

[15] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–57.
[16] Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–39.
[17] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35.
[18] Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–29.
[19] Eli Lilly Press Release., https://investor.lilly.com/node/39796/pdf; 2018 [accessed 31 May 2018].
[20] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2018. http://dx.doi.org/10.1056/NEJMoa1812389 [Epub ahead of print].
[21] Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. Diabetes Care 2000;23:962–8.
[22] Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–93.
[23] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–701.
[24] Lau J, Bloch P, Schaffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem 2015;58:7370–80.
[25] Novo Nordisk A/S. Novo Nordisk Receives FDA Approval of OZEMPIC® (semaglutide) Injection For the Treatment of Adults with Type 2 Diabetes, http://press.novonordisk-us.com/2017-12-5-Novo-Nordisk-Receives-FDA-Approval-of-OZEMPIC-R-semaglutide-Injection-For-the-Treatment-of-Adults-with-Type-2-Diabetes; [accessed Mar 5, 2018].
[26] Novo Nordisk A/S. Ozempic® (semaglutide) approved in the EU for the treatment of type 2 diabetes, https://www.novonordisk.com/bin/getPDF.2167679. pdf; 2018 [accessed 31 May 2018].
[27] Novo Nordisk Canada Inc. Ozempic® approved in Canada for the treatment of adults with type 2 diabetes, https://www.newswire.ca/news-releases/ozempic-approved-in-canada-for-the-treatment-of-adults-with-type-2-diabetes-668432133.html; 2018 [accessed 31 May 2018].
[28] Novo Nordisk. Ozempic® approved in Japan for the treatment of type 2 diabetes, https://www.novonordisk.com/bin/getPDF.2178681.pdf [accessed 31/05/2018].
[29] Donath MY, Burcelin R. GLP-1 effects on islets: hormonal, neuronal, or paracrine? Diabetes Care 2013;36(Suppl 2):S145–8.
[30] Secher A, Jelsing J, Baquero AF, Hecksher-Sorensen J, Cowley MA, Dalboge LS, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest 2014;124:4473–88.
[31] Blundell J, Finlayson G, Axelsen MB, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017;19:1242–51.
[32] Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 2017;5:251–60.
[33] Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbol JD, Jacobsen SH, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol 2017;5:341–54.
[34] Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care 2018;41:258–66.
[35] Aroda VR, Bain SC, Cariou B, Piletic M, Rose L, Axelsen M, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017;5:355–66.
[36] Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab 2018;103:2291–301.
[37] Pratley RE, Aroda VR, Lingvay I, Ludemann J, Andreassen C, Navarria A, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol 2018;6:275–86.
[38] Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–95.
[39] US Department of Health and Human Services Food and Drug Administration. Guidance for Industry Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf; 2008 [accessed 31 May 2018].
[40] Rodbard H, Bellary S, Hramiak I, Seino Y, Silver R, Bergan EQ, et al. Responder analysis of subjects achieving HbA1c ≥1% and weight loss ≥5% across SUSTAIN 1-5 clinical trials. ePoster number 802. Lisbon 2017 EASD, https://www.easd.org/myeasd/home.html#!resources/responder-analysis-of-subjects-achieving-hba-sub-1c-sub-1-and-weight-loss-5-across-sustain-1-5-clinical-trials-86583438-fc4a-46b6-b123-8829251827b1; 2017 [accessed 31 May 2018].
[41] Ahrén B, Atkin SL, Charpentier G, Warren ML, Wilding JPH, Birch S, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. Diabetes Obes Metab 2018;20:2210–9.
[42] DeVries JH, Desouza C, Bellary S, Unger J, Bangsgaard EO, et al. More semaglutide-treated subjects achieved HbA_{1c} below 7.0% without weight gain, hypoglycaemia, and gastrointestinal adverse events vs. comparators in the SUSTAIN 1–5 trials. European Association for the Study of Diabetes (EASD) – 53rd Annual Meeting 2017 [Poster 815].
[43] Bain S, Araki E, Desouza C, Garg S, Rose L, Tsoukas G, et al. Semaglutide reduces HbA_{1c} across baseline HbA_{1c} subgroups in the SUSTAIN 1–5 clinical trials. 77th Scientific Sessions of the American Diabetes Association 2017.
[44] Atkin S, Woo V, de la Rosa R, Wilding J, Yamada Y, et al. The impact of gastrointestinal adverse events on weight loss with semaglutide in subjects with type 2 diabetes. European Association for the Study of Diabetes (EASD) – 53rd Annual Meeting 2017 [Poster 821].
[45] Vilsbøll T, Bain SC, Leiter LA, Lingvay I, Matthews D, Simó R, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab 2018;20:889–97.
[46] Intarcia Therapeutics press release. Intarcia announces successful cardiovascular safety results in phase 3 FREEDOM-CVO Trial for ITCA 650, an investigational therapy for type 2 diabetes, https://www.intarcia.com/media/press-releases/2016-may-6-cardiovascular-safety.html [Accessed October, 2017].
[47] Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT-2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2018 [pii: S0140-6736(18)32590-X; Epub ahead of print].
[48] Health Canada. OZEMPIC (semaglutide) injection product monograph, Jan 09, 2018, http://www.novonordisk.ca/content/dam/Canada/AFFILIATE/www-novonordisk-ca/OurProducts/PDF/ozempic-product-monograph.pdf; 2018 [accessed 31 May 2018].
[49] US Food and Drug Administration. OZEMPIC (semaglutide) injection prescribing information; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf; 2017 [accessed 31 May 2018.
[50] Summary product characteristics Ozempic, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004174/WC500244163.pdf [accessed April 2018].
[51] Scheen AJ. GLP-1 receptor agonists and cardiovascular protection: a class effect or not? Diabetes Metab 2018;44:193–6.
[52] Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hanselmann A, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail 2017;19:69–77.
[53] Vilsbøll TG, Gumprecht J, Silver RJ, Hansen T, Pettersson J, Wilding J. Semaglutide treatment and renal function in the SUSTAIN 6 trial. 77th Scientific Sessions of the American Diabetes Association 2018 [Poster 1084-P].
[54] Marbury T, Flint A, Segel S, Lindegaard M, Lasseter K. Pharmacokinetics and tolerability of a single dose of semaglutide, a once-weekly human GLP-1 analog, in subjects with and without renal impairment. Clin Pharmacokinet 2017;56:1381–90.
[55] Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. Ther Adv Endocrinol Metab 2015;6:19–28.
[56] Warren M, Chaykin L, Trachtenbarg D, Nayak G, Wijayasinghe N, Cariou B. Semaglutide as a therapeutic option for elderly patients with type 2 diabetes: Pooled analysis of the SUSTAIN 1-5 trials. Diabetes Obes Metab 2018;20:2291–7.
[57] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[58] Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
[59] Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drugs Context 2015;4:212283.