Received: 5 February 2020 | Revised: 30 April 2020 | Accepted: 13 May 2020

DOI: 10.1111/jcpt.13225

REVIEW ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes

Jennifer Trujillo PharmD, BCPS, CDCES, BC-ADM

Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO, USA

Correspondence
Jennifer Trujillo, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, 12850 E. Montview Blvd. M/S C238, Aurora, CO 80045, USA.
Email: jennifer.trujillo@cuanschutz.edu

Funding information
Novo Nordisk Inc., Plainsboro, New Jersey, USA, funded the medical writing support for this review.

Abstract

What is known and objective: In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) including once-weekly (QW) formulations have been incorporated into type 2 diabetes (T2D) clinical guidelines, making it essential that pharmacists and healthcare professionals (HCPs) have a clear understanding of their safety profiles. Currently, three QW GLP-1 RAs are approved and marketed in the United States for the treatment of T2D: dulaglutide, exenatide extended-release and semaglutide. This review provides pharmacists and HCPs with collated data related to potential safety and tolerability issues when patients use QW GLP-1 RAs, enabling patient education and treatment optimization.

Methods: This is a narrative review comparing the safety and tolerability of the three QW GLP-1 RAs, using data from Phase 3 clinical trials. Extracted safety data included gastrointestinal (GI) adverse events (AEs), hypoglycaemia, injection-site reactions, pancreatitis, neoplasms, gallbladder events, and diabetic retinopathy (DR) and/or its complications (DRCs).

Results and discussion: A total of 30 trials were identified for inclusion; eight were head-to-head trials involving another GLP-1 RA; of these, six compared GLP-1 RAs with different dosing regimens (QW vs once-daily or twice-daily), and two were direct QW vs QW GLP-1 RA comparisons. The most commonly reported AEs were GI events (notably nausea, vomiting and diarrhoea), but there was variation between the three QW drugs. These were generally mild-to-moderate in severity and transient. Risk of hypoglycaemia, injection-site reactions, pancreatitis, neoplasms and gallbladder events was generally low across the GLP-1 RAs investigated. Overall rates of DR or DRC were low across the trials. Only in one trial (SUSTAIN 6) there were significantly more DRC events reported in patients treated with QW semaglutide (3.0%) compared with placebo (1.8%). This was likely due to the rapid improvement in glucose control in patients with pre-existing DR enrolled within that trial.

What is new and conclusion: This review puts the latest clinical data from the marketed QW GLP-1 RAs into context with results from older Phase 3 trials, to enable pharmacists and HCPs to make informed treatment decisions. Each of the three QW

GLP-1 RAs has their own safety profile, which should be considered when choosing the optimal treatment for patients.

KEYWORDS
dulaglutide, exenatide, GLP-1 RA, safety, semaglutide, tolerability, type 2 diabetes

1 | WHAT IS KNOWN AND OBJECTIVE

Diabetes mellitus has emerged as one of the leading causes of disability worldwide, positioned in 2017 as the fourth cause of age-standardized years-lived-with-disability (YLD).[1] Globally, in 2017, there were approximately 476 million cases of diabetes and 23 million new cases of diabetes, of which 463 million and 22.5 million were type 2 diabetes (T2D), respectively.[1] YLD was reported as over 38 million, with the rate increasing by 30% from 2007 to 2017,[1] which demonstrates the importance of understanding this disease and treating it optimally.

T2D is caused by a combination of insulin resistance, pancreatic beta-cell dysfunction and inappropriate glucagon secretion.[2] Pharmacological intervention is required for many patients with T2D to achieve and maintain glycaemic control.[3,4] However, risk of hypoglycaemia is an important barrier to glycaemic control, with a high cost burden in terms of morbidity, health-related quality of life (HRQoL) and health resource utilization.[5] Moreover, some diabetes treatments may confer risks of hypoglycaemic events and body weight gain that also negatively impact HRQoL, thus adding to the disease burden.[5] To address these different facets of T2D and its treatment, guidelines recommend taking an individualized approach when prescribing anti-diabetic agents for patients with T2D.[4] Clinicians, therefore, need to balance patient characteristics (such as the blood glucose levels, presence of comorbidities, duration of T2D and obesity status) with the effectiveness and safety/tolerability of the treatments.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin-based therapies that promote glucose control through mimicking GLP-1 and activating GLP-1 receptor mechanisms, thus increasing glucose-dependent insulin secretion, inhibiting glucagon secretion and decreasing gastric emptying.[6,7] GLP-1 RAs have been shown to improve glycaemic control and aid weight loss, with a lower risk of hypoglycaemia compared with other glucose-lowering treatments.[8,9] With the results from cardiovascular outcomes trials (CVOTs), they are now one of the preferred treatment options for people with T2D and established atherosclerotic cardiovascular disease (CVD).[3,4,10]

Currently, the GLP-1 RAs marketed for the treatment of T2D in the United States (US) are: dulaglutide, exenatide (available in two formulations: twice-daily [BID] and extended-release [ER]), liraglutide, lixisenatide and semaglutide (available in two formulations: subcutaneous [s.c.] and oral).[11-17] There are variations in the dosing frequency from BID to once-daily (QD) or to once-weekly (QW), and administration (s.c. injection[11-16] or tablet formation[17]). The QW GLP-1 RAs currently marketed are dulaglutide (0.75 or 1.5 mg QW), exenatide ER (2 mg QW) and semaglutide (0.5 or 1 mg QW).[11,12,16]

Although they share similar underlying mechanisms, differences in structure, receptor affinity and pharmacokinetics between the QW GLP-1 RAs result in varying safety profiles.[18,19] Due to the changes in the guidelines, it is important for all involved in patient care to fully understand the safety and tolerability profiles of QW GLP-1 RAs.[3,4,10] This narrative review compares the safety and tolerability of the three licensed and marketed QW GLP-1 RAs across their Phase 3 clinical programmes to provide pharmacists and healthcare professionals (HCPs) with an increased understanding of their potential safety and tolerability.

2 | METHODS

This is a narrative review of the safety and tolerability of QW GLP-1 RAs in patients with T2D, derived from their Phase 3 clinical trials. Articles were identified through PubMed using the search terms ['GLP-1 RA' OR 'glucagon-like peptide-1 receptor agonist'] AND ['type 2 diabetes' OR T2D] AND [Phase 3] AND [dulaglutide OR 'exenatide ER' OR semaglutide] AND 'Phase 3' from 1 January 2001 to 31 May 2019. The results of this search were filtered for those publications directly reporting results from clinical trials on dulaglutide, exenatide ER and semaglutide enrolling patients with T2D, and comparing these GLP-1 RAs with placebo or any active comparator. Other trials were included if they were part of the clinical programmes for these QW GLP-1 RAs and published between May 2019 and November 2019. Articles were not included if they were case reports, books and not published in English. Related primary publications and review articles were also searched. The review focuses on the currently available and marketed QW GLP-1 RAs dulaglutide, exenatide ER and semaglutide. The QW GLP-1 RA albiglutide was not included in this review, as it was withdrawn from the market in 2018 for commercial reasons.[20]

3 | RESULTS AND DISCUSSION

3.1 | Trials included

A total of 30 trials in patients with T2D (including dulaglutide trials AWARD-1 to -10 and REWIND, exenatide ER trials DURATION-1 to -8 and EXSCEL, and semaglutide trials SUSTAIN 1 to 10) were identified for inclusion in this review (Table 1). Of these, eight were

TABLE 1 QW GLP-1 RA Phase 3 trials included in this review

Trial	Treatment arms	Background therapies	Study duration	Study type	Randomization ratio	Number of patients	Location(s)
Dulaglutide trials							
AWARD-2[28]	Dulaglutide QW (1.5 mg or 0.75 mg) vs insulin glargine QD	Glimepiride and metformin	78 wk in total (primary endpoint at 52 wk)	Randomized, open-label	1:1:1	810	Multinational
AWARD-3[33]	Dulaglutide QW (1.5 mg or 0.75 mg) vs metformin QD (2000 mg)	SOC/≥1 oral anti-glycaemic medication	52 wk in total (primary endpoint at 26 wk)	Randomized, double-blind	1:1:1	807	Multinational
AWARD-4[29]	Dulaglutide QW (1.5 mg or 0.75 mg) vs insulin glargine QD	Insulin lispro ± metformin	52 wk in total (primary endpoint at 26 wk)	Randomized, open-label	1:1:1	884	Multinational
AWARD-5[35]	Dulaglutide QW (1.5 mg or 0.75 mg) vs sitagliptin QD (100 mg) or placebo	Metformin	104 wk in total (primary endpoint at 52 wk)	Randomized, open-label, double-blind, placebo-controlled	2:2:2:1	1098	Multinational
AWARD-7[30]	Dulaglutide QW (1.5 mg or 0.75 mg) vs insulin glargine QD	Insulin lispro	52 wk in total (primary endpoint at 26 wk)	Randomized, open-label	1:1:1	577	Multinational
AWARD-8[47]	Dulaglutide QW (1.5 mg) vs placebo	Glimepiride or sulphonylurea	24 wk treatment	Randomized, double-blind	4:1	300	Multinational
AWARD-9[46]	Dulaglutide QW (1.5 mg) vs placebo	Insulin glargine	28 wk treatment	Randomized, double-blind	1:1	300	Multinational
AWARD-10[48]	Dulaglutide QW (1.5 mg or 0.75 mg) vs placebo	SGLT2i ± metformin	24 wk treatment	Randomized, double-blind, placebo-controlled	1:1	424	Multinational
[a]REWIND[21]	Dulaglutide QW (1.5 mg) vs placebo	SOC ± basal insulin	Up to 8 y; median follow-up 5.4 y	Randomized, double-blind, placebo-controlled	1:1	9901	Multinational
Exenatide trials							
DURATION-2[36]	Exenatide QW (2 mg) vs sitagliptin QD (100 mg) vs pioglitazone QD (45 mg)	Metformin	26 wk treatment	Randomized, double-blind	1:1:1	514	US, India, Mexico
DURATION-3[31]	Exenatide QW (2 mg) vs insulin glargine QD	Metformin/ metformin + sulphonylurea	26 wk treatment	Randomized, open-label	1:1	456	Multinational
DURATION-4[34]	Exenatide QW (2 mg) vs metformin QD (2000 mg) vs pioglitazone QD (45 mg) vs sitagliptin QD (100 mg)	SOC	26 wk treatment	Randomized, open-label	1:1:1:1	820	Multinational
DURATION-7[49]	Exenatide QW (2 mg) vs placebo	Insulin glargine ± metformin	28 wk treatment	Randomized, double-blind, placebo-controlled	1:1	464	Multinational
DURATION-8[50]	Exenatide QW (2 mg) + dapagliflozin QD (10 mg) vs exenatide QW (2 mg) vs dapagliflozin QD (10 mg)	Metformin	28 wk treatment	Randomized, double-blind, active-controlled	1:1:1	695	Multinational
[a]EXSCEL[22]	Exenatide QW (2 mg) vs placebo	Insulin ± up to 2 oral glucose-lowering drugs	Event-driven trial; median follow-up 3.2 y	Randomized, double-blind, placebo-controlled	1:1	14 752	Multinational

(Continues)

TABLE 1 (Continued)

Trial	Treatment arms	Background therapies	Study duration	Study type	Randomization ratio	Number of patients	Location(s)
Semaglutide (subcutaneous injection) trials							
SUSTAIN 1[42]	Semaglutide QW (1 mg or 0.5 mg) vs placebo (1 mg or 0.5 mg)	SOC	30 wk treatment	Randomized, double-blind	2:2:1:1	387	Multinational
SUSTAIN 2[37]	Semaglutide QW (1 mg or 0.5 mg) vs sitagliptin QD (100 mg)	Metformin, pioglitazone, rosiglitazone, metformin ± pioglitazone or metformin ± rosiglitazone	56 wk treatment	Randomized, double-blind	2:2:1:1	1231	Multinational
SUSTAIN 4[32]	Semaglutide QW (1 mg or 0.5 mg) vs insulin glargine QD	Metformin ± sulphonylurea	30 wk treatment	Randomized, open-label	1:1:1	1089	Multinational
SUSTAIN 5[44]	Semaglutide QW (1 mg or 0.5 mg) vs placebo (1 mg or 0.5 mg)	Basal insulin ± metformin	30 wk treatment	Randomized, double-blind, placebo-controlled	2:2:1:1	397	Multinational
[a]SUSTAIN 6[23]	Semaglutide QW (1 mg or 0.5 mg) vs placebo (1 mg or 0.5 mg)	Insulin ± basal or premixed insulin	109 wk in total (primary endpoint at 104 wk)	Randomized, double-blind, placebo-controlled	1:1:1:1	3297	Multinational
SUSTAIN 8[38]	Semaglutide QW (1 mg) vs canagliflozin QD (300 mg)	Metformin	52 wk treatment	Randomized, double-blind	1:1	788	Multinational
SUSTAIN 9[51]	Semaglutide QW (1 mg) vs placebo	SGLT2i, metformin, sulphonylurea	30 wk treatment	Randomized, double-blind, placebo-controlled	1:1	302	Multinational
Head-to-head trials: QW vs QD or BID							
AWARD-1[39]	Dulaglutide QW (1.5 mg or 0.75 mg) vs exenatide BID (10 μg) vs Placebo	Pioglitazone and metformin	52 wk in total (primary endpoint at 26 wk)	Randomized, placebo-controlled	2:2:2:1	978	Mexico, Argentina, US
AWARD-6[40]	Dulaglutide QW (1.5 mg) vs liraglutide QD (1.8 mg)	Metformin	26 wk treatment	Randomized, open-label	1:1	599	Multinational
DURATION-1[24,25]	Exenatide QW (2 mg) vs exenatide BID (10 μg)	Sulphonylurea	30 wk treatment	Randomized, open-label, non-inferiority	1:1	295	Canada, US
DURATION-5[26]	Exenatide QW (2 mg) vs exenatide BID (10 μg)	SOC or metformin, sulphonylurea, thiazolidinedione, or a combination of these	24 wk treatment	Randomized, open-label	1:1	254	US
DURATION-6[41]	Exenatide QW (2 mg) vs liraglutide QD (1.8 mg)	Sulphonylurea	26 wk treatment	Randomized, open-label	1:1	912	Multinational
SUSTAIN 10[52]	Semaglutide QW (1 mg) vs liraglutide QD (1.2 mg)	SGLT2i, metformin, sulphonylurea	30 wk treatment	Randomized, open-label	1:1	577	Multinational

(Continues)

TABLE 1 (Continued)

Trial	Treatment arms	Background therapies	Study duration	Study type	Randomization ratio	Number of patients	Location(s)
Head-to-head trials: QW vs QW							
SUSTAIN 3[43]	Semaglutide QW (1 mg) vs exenatide QW (2 mg)	Metformin ± thiazolidinedione, ± sulphonylurea	56 wk treatment	Randomized, open-label	1:1	813	Multinational
SUSTAIN 7[45]	Semaglutide QW (1 mg or 0.5 mg) vs dulaglutide QW (1.5 mg or 0.75 mg)	Metformin	40 wk treatment	Randomized, open-label	1:1:1:1	1201	Multinational

Abbreviations: BID, twice-daily; CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; QD, once-daily; QW, once-weekly; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SOC, standard of care; wk, weeks; y, years.

[a]These studies are CVOTs, with longer follow-up times and larger patient populations than the other studies in this table.

head-to-head GLP-1 RA trials involving different dosing regimens (AWARD-1 and -6, DURATION-1, -5 and -6, and SUSTAIN 3, 7 and 10). Only two of these head-to-head trials involved direct QW GLP-1 RA comparisons (SUSTAIN 3 and 7). Three of the trials included in this review (REWIND, EXSCEL and SUSTAIN 6)[21-23] are large CVOTs, with longer follow-up than the other short-term glycaemic control trials reported here.

The majority of trials were multinational and multicentre, with the exception of DURATION-1, located in the US/Canada,[24,25] and DURATION-5, located in the US only.[26] Eligibility criteria and background treatment varied among studies, with most maintaining prestudy treatments including metformin, insulin glargine and sulphonylurea (Table 1).

To ensure relevance of this review to pharmacists and HCPs, it focuses on the adverse events (AEs) reported most frequently and those recognized as safety risks with GLP-1 RAs.

3.2 | GI AEs (nausea, vomiting and diarrhoea)

Treatment-emergent gastrointestinal (GI) AEs are well-recognized GLP-1 RA AEs.[27] All GLP-1 RAs increased the proportion of patients experiencing nausea, vomiting and diarrhoea, specifically nausea, in comparison with placebo, although there was variability within the QW GLP-1 RA class (Table 2). Rates with GLP-1 RAs were also found to be higher than with other glucose-lowering agents, including insulin,[28-32] metformin,[33,34] sitagliptin[34-37] and canagliflozin.[38] Nausea over time was not reported in all trials; where reported, it was mostly transient, occurring primarily in the first few weeks of treatment and resolving or stabilizing over time.[28,32,35,37,39-45]

Examining each of the three QW GLP-1 RAs individually, GI events were reported more frequently with dulaglutide than comparator arms. For both doses of dulaglutide, 8%-29% of patients reported nausea (0%-28% for comparators), 4%-18% reported vomiting (0%-12% for comparators) and 6%-17% reported diarrhoea (0%-14% for comparators) across the AWARD trials.[28-30,33,35,39,40,46-48] The GI risk appeared to be dose-related for dulaglutide, with greater risk associated with higher doses.[28,29,33,35,39,48] GI events were only reported as a combined group of diarrhoea, nausea, constipation and vomiting in REWIND, and again the incidence differed between dulaglutide and placebo (47% vs 34%, respectively).[21]

For exenatide ER, a similar pattern was evident for many of the events: 5%-26% of patients reported nausea (1%-21% for comparators), 0.4%-11% reported vomiting (1%-11% for comparators) and 4%-18% reported diarrhoea (3%-13% for comparators).[31,34,36,41,49,50] GI events were more generally common with exenatide BID than exenatide ER in DURATION-1 and -5.[24,26] EXSCEL only reported specifically on GI AEs leading to discontinuation, and these were higher in the exenatide ER arm (333 patients [4.5%]) compared with placebo (109 patients [1.5%]).[22]

The frequency and rate of GI AEs were higher with semaglutide vs all comparators for both doses. For the 1 mg dose, 2%-23% of

TABLE 2 Patients experiencing GI events (nausea, vomiting and diarrhoea) in QW GLP-1 RA Phase 3 trials

Trial	Treatment arms	Number of patients	Patients, n (%)			Discontinuation[a] due to AEs, n (%)
			Nausea	Vomiting	Diarrhoea	
Dulaglutide trials						
AWARD-1[39]	Dulaglutide QW 1.5 mg	279	81 (29)	47 (17)	36 (13)	9 (3)
	Dulaglutide QW 0.75 mg	280	47 (17)*	17 (6)*	26 (9)	4 (1)
	Exenatide BID 10 μg	276	77 (28)	33 (12)	21 (8)	10 (4)
AWARD-2[28]	Dulaglutide QW 1.5 mg	273	42 (15.4)**	18 (6.6)*	29 (10.6)	9 (3.3)
	Dulaglutide QW 0.75 mg	272	21 (7.7)**	10 (3.7)	25 (9.2)	8 (2.9)
	Insulin glargine QD	262	4 (1.5)	3 (1.1)	15 (5.7)	5 (1.9)
AWARD-3[33]	Dulaglutide QW 1.5 mg	269	53 (19.7)	26 (9.7)	30 (11.2)	14 (5.2)
	Dulaglutide QW 0.75 mg	270	31 (11.5)	20 (7.4)	21 (7.8)	8 (3.0)
	Metformin QD 2000 mg	268	43 (16.0)	13 (4.9)	37 (13.8)	12 (4.5)
AWARD-4[29]	Dulaglutide QW 1.5 mg	295	76 (26)**	36 (12)**	49 (17)**	31 (11)
	Dulaglutide QW 0.75 mg	293	52 (18)**	31 (11)**	46 (16)*	22 (8)
	Insulin glargine QD	296	10 (3)	5 (2)	18 (6)	12 (4)
AWARD-5[35]	Dulaglutide QW 1.5 mg	304	53 (17)**	39 (13)**	44 (15)**	33 (11)
	Dulaglutide QW 0.75 mg	302	42 (14)**	23 (8)*	30 (10)**	23 (8)
	Sitagliptin QD 100 mg	315	16 (5)	7 (2)	9 (3)	30 (10)
AWARD-6[40]	Dulaglutide QW 1.5 mg	299	61 (20)	21 (7)	36 (12)	18 (6)
	Liraglutide QD 1.8 mg	300	54 (18)	25 (8)	36 (12)	18 (6)
AWARD-7[30]	Dulaglutide QW 1.5 mg	192	38 (20)**	26 (14)*	33 (17)*	24 (13)
	Dulaglutide QW 0.75 mg	190	27 (14)*	16 (8)	30 (16)*	19 (10)
	Insulin glargine QD	194	9 (5)	9 (5)	14 (7)	12 (6)
AWARD-8[47]	Dulaglutide QW 1.5 mg	239	25 (10.5)*	NR	20 (8.4)*	25 (10.4)
	Placebo	60	0		0	4 (6.7)
AWARD-9[46]	Dulaglutide QW 1.5 mg	150	18 (12.0)**	9 (6.0)*	17 (11.3)*	6 (4.0)
	Placebo	150	2 (1.3)	0	6 (4.0)	2 (1.3)
AWARD-10[48]	Dulaglutide QW 1.5 mg	142	21 (15)	NR	8 (6)	4 (3)
	Dulaglutide QW 0.75 mg	141	7 (5)		14 (10)	0
	Placebo	140	5 (4)		4 (3)	0
Exenatide trials						
DURATION-1[24]	Exenatide QW 2 mg	148	39 (26.4)	16 (10.8)	20 (13.5)	9 (6)
	Exenatide BID 10 μg	145	50 (34.5)	27 (18.6)	19 (13.1)	7 (5)
DURATION-2[36]	Exenatide QW 2 mg	160	38 (24)	18 (11)	29 (18)	11 (7)
	Sitagliptin QD 100 mg	166	16 (10)	4 (2)	16 (10)	5 (3)
	Pioglitazone QD 45 mg	165	8 (5)	5 (3)	12 (7)	6 (4)
DURATION-3[31]	Exenatide QW 2 mg	233	30 (13)	10 (4)	20 (9)	12 (5)
	Insulin glargine QD	223	3 (1)	3 (1)	8 (4)	2 (1)
DURATION-4[34]	Exenatide QW 2 mg	248	28 (11.3)	NR	27 (10.9)	6 (2.4)
	Metformin QD 2000 mg	246	17 (6.9)		31 (12.6)	6 (2.4)
	Pioglitazone QD 45 mg	163	7 (4.3)		6 (3.7)	5 (3.1)
	Sitagliptin QD 100 mg	163	6 (3.7)		9 (5.5)	1 (0.6)
DURATION-5[26]	Exenatide QW 2 mg	129	18 (14.0)	6 (4.7)	12 (9.3)	6 (4.9)
	Exenatide BID 10 μg	123	43 (35.0)	11 (8.9)	5 (4.1)	6 (4.9)
DURATION-6[41]	Exenatide QW 2 mg	461	43 (9)	17 (4)	28 (6)	12 (3)
	Liraglutide QD 1.8 mg	450	93 (21)	48 (11)	59 (13)	25 (6)

(Continues)

TABLE 2 (Continued)

Trial	Treatment arms	Number of patients	Patients, n (%)			Discontinuation[a] due to AEs, n (%)
			Nausea	Vomiting	Diarrhoea	
DURATION-7[49]	Exenatide QW 2 mg	232	12 (5.2)	1 (0.4)	11 (4.7)	9 (3.9)
	Placebo	231	9 (3.9)	3 (1.3)	8 (3.5)	4 (1.7)
DURATION-8[50]	Exenatide QW 2 mg + dapagliflozin QD 10 mg	231	12 (5)	NR	10 (4)	9 (4)
	Exenatide QW 2 mg	230	17 (7)		13 (6)	11 (5)
	Dapagliflozin QD 10 mg	233	7 (3)		7 (3)	5 (2)
Semaglutide trials						
SUSTAIN 1[42]	Semaglutide QW 1 mg	130	2 (2)	2 (2)	0	7 (5)
	Semaglutide QW 0.5 mg	128	2 (2)	1 (<1)	3 (2)	8 (6)
	Placebo	129	1 (<1)	0	0	3 (2)
SUSTAIN 2[37]	Semaglutide QW 1 mg	409	12 (3)	10 (2)	9 (2)	39 (10)
	Semaglutide QW 0.5 mg	409	11 (3)	3 (1)	10 (2)	33 (8)
	Sitagliptin QD 100 mg	407	2 (<1)	0	0	12 (3)
SUSTAIN 3[43]	Semaglutide QW 1 mg	404	90 (22.3)	29 (7.2)	46 (11.4)	38 (9.4)
	Exenatide QW 2 mg	405	48 (11.9)	25 (6.2)	34 (8.4)	29 (7.2)
SUSTAIN 4[32]	Semaglutide QW 1 mg	360	7 (2)	7 (2)	9 (3)	27 (8)
	Semaglutide QW 0.5 mg	362	3 (1)	3 (1)	1 (<1)	20 (6)
	Insulin glargine QD	360	0	0	0	4 (1)
SUSTAIN 5[44]	Semaglutide QW 1 mg	131	22 (16.8)	15 (11.5)	9 (6.9)	8 (6.1)
	Semaglutide QW 0.5 mg	132	15 (11.4)	8 (6.1)	6 (4.5)	6 (4.5)
	Placebo 1 mg or 0.5 mg	133	6 (4.5)	4 (3.0)	2 (1.5)	1 (0.8)
SUSTAIN 6[23]	Semaglutide QW 1 mg	822	180 (21.9)	122 (14.8)	151 (18.4)	119 (14.5)
	Semaglutide QW 0.5 mg	826	143 (17.3)	87 (10.5)	148 (17.9)	95 (11.5)
	Placebo 1 mg	825	67 (8.1)	34 (4.1)	87 (10.5)	63 (7.6)
	Placebo 0.5 mg	824	62 (7.5)	43 (5.2)	98 (11.9)	47 (5.7)
SUSTAIN 7[45]	Semaglutide QW 1 mg	300	63 (21)	31 (10)	41 (14)	29 (10)
	Semaglutide QW 0.5 mg	301	68 (23)	31 (10)	43 (14)	24 (8)
	Dulaglutide QW 1.5 mg	299	60 (20)	29 (10)	53 (18)	20 (7)
	Dulaglutide QW 0.75 mg	299	39 (13)	12 (4)	23 (8)	14 (5)
SUSTAIN 8[38]	Semaglutide QW 1 mg	394	89 (23)	50 (13)	60 (15)	38 (10)
	Canagliflozin QD 300 mg	394	26 (7)	9 (2)	37 (9)	20 (5)
SUSTAIN 9[51]	Semaglutide QW 1 mg	150	29 (19.3)	14 (9.3)	17 (11.3)	13 (8.7)
	Placebo	151	5 (3.3)	3 (2.0)	9 (6.0)	3 (2.0)
SUSTAIN 10[52]	Semaglutide QW 1 mg	290	127 (43.9)	30 (10.4)	45 (15.6)	33 (11.4)
	Liraglutide QD 1.5 mg	287	45 (15.6)	23 (8.0)	35 (12.2)	19 (6.6)

Abbreviations: BID, twice-daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NR, not reported; QD, once-daily; QW, once-weekly.

[a]Discontinuation from study treatment and/or study itself, depending on reported data.

*$P < .05$

**$P \leq .001$.

patients reported nausea (0%-20% for comparators), 2%-15% reported vomiting (0%-10% for comparators) and 0%-18% reported diarrhoea (0%-18% for comparators).[23,32,37,38,42-45,51,52]

In head-to-head QW GLP-1 RA trials, more patients reported nausea, vomiting and diarrhoea with semaglutide 1 mg vs exenatide ER 2 mg in SUSTAIN 3,[43] and for both semaglutide doses (0.5 and 1 mg) and dulaglutide 1.5 mg vs dulaglutide 0.75 mg in SUSTAIN 7[45] (Table 2). When using the highest dose available of these three QW GLP-1 RAs, it appears that exenatide ER has a more favourable GI AE profile compared to dulaglutide or semaglutide.

As an indicator of the patient-drug tolerability resulting from AEs across all of these QW GLP-1 RA trials, discontinuations from study

treatment due to AEs were examined (Table 2). Discontinuation rates were 0%-15% of patients, dependent on treatment group, with exenatide QW tending to have slightly lower rates than semaglutide or dulaglutide (Table 2). Serious GI AEs were not reported consistently across the trials, with many just reporting serious AEs overall in these primary trial publications, and so this information could not be compared here.

3.3 | Hypoglycaemia

As mentioned, hypoglycaemia is an important consideration when treating patients with T2D. Patients experienced more hypoglycaemic events in trials that allowed concomitant use of insulins and sulphonylureas than in trials that did not allow these background treatments (Table 3).[21-24,26,29-32,43,44,46,47,49,51,52]

Evaluation of severe/major hypoglycaemia differed across trials. For the AWARD trials, this was as per American Diabetes Association (ADA) classification,[53,54] whereas in the DURATION and SUSTAIN trials, this was per the ADA classification and also included blood glucose-confirmed hypoglycaemia (defined as <3.1 mmol/L or 56 mg/dL) in some of the trials. The proportion of patients experiencing severe/major hypoglycaemia was generally <1% across all the AWARD and DURATION trials (Table 3), with the exception of AWARD-4 and -7, both of which allowed patients to use background insulins.[29,30] In other trials, severe hypoglycaemia was slightly higher, reported in 1.3% of patients receiving dulaglutide in REWIND, 3.4% of patients receiving exenatide ER in EXSCEL,[21,22] and in ≤2% of patients receiving semaglutide in SUSTAIN 1, 2, 7, 8 and 10.[37,38,42,45,52] Higher rates were reported in the other SUSTAIN trials (3%-23%), likely as a result of patients continued use of background insulins and/or sulphonylureas.[23,32,43,51]

In the head-to-head QW vs QD/BID GLP-1 RA trials, hypoglycaemia rates were lower in patients receiving dulaglutide 1.5 mg than those receiving exenatide BID in AWARD-1,[39] but higher than reported with liraglutide in AWARD-6.[40] Similar hypoglycaemia rates were reported with exenatide ER vs BID in DURATION-1 and -5.[24,26] In DURATION-6, rates were higher with exenatide ER than liraglutide.[41] In head-to-head QW GLP-1 RA trials, similar rates of severe hypoglycaemia were reported in patients receiving semaglutide and exenatide ER, and semaglutide and dulaglutide in SUSTAIN 3 and 7, respectively.[43,45] Therefore, there appears to be no difference between these three QW GLP-1 RAs in terms of hypoglycaemia rates. Based on the head-to-head trials of QW vs QD/BID GLP-1 RAs, it appears that hypoglycaemia rates with QW agents may be lower than with exenatide BID but higher than with liraglutide QD.

3.4 | Injection-site reactions

Injection-site reactions (ISRs) were reported differently across the trials (Table 3), ranging from a single event (eg injection-site nodule, injection-site pruritus, injection-site bruising) to any injection-site event, making direct comparisons difficult. The AWARD trials generally reported ISRs,[28-30,33,35,39,46-48] whereas the DURATION trials reported injection-site nodules,[34,41,49,50] pruritus,[24,36] erythema[41] or ISRs.[31] For the SUSTAIN trials, ISRs were reported in SUSTAIN 6 and 7,[23,45] whereas SUSTAIN 3 reported injection-site nodules.[43] It is important to keep these differences in definition in mind, as the data across trials are compared.

The majority of the AWARD trials reported low rates of ISRs (<1%), with the exception of AWARD 3[33] (which reported ISRs in 3.7%, 2.2% and 1.5% of patients receiving dulaglutide 1.5 mg, dulaglutide 0.75 mg and metformin/placebo, respectively). In the head-to-head trials, the percentage of patients reporting ISRs were the same for dulaglutide and comparator arms.[39,40]

In DURATION-2, -3,-4,-7 and -8, patients on the exenatide ER arm reported higher ISR rates vs the competitor arm, ranging from 8% to 13%.[31,34,36,49,50] In the head-to-head trials, ISRs were more common with exenatide ER than BID in DURATION-1 and -5.[24,26] Injection-site nodules, pruritus and erythema were reported more commonly with exenatide ER than liraglutide in DURATION-6 (Table 3).[41]

Of the SUSTAIN trials, only the QW head-to-head trials SUSTAIN 3 and 7 reported ISRs.[43,45] More patients reported ISRs with exenatide ER (22%) vs semaglutide (1.2%) in SUSTAIN 3,[43] whereas the percentages of ISRs reported by patients treated with dulaglutide (1%-3%) vs semaglutide (1%-2%) were comparable in SUSTAIN 7 (Table 3).[45]

Across the three QW GLP-1 RAs, it appears that exenatide ER resulted in the greatest number of ISRs compared with dulaglutide and semaglutide, which had similar numbers.

3.5 | Pancreatitis

Regulatory authorities have expressed concerns regarding the use of GLP-1 RAs and the potential risk of acute pancreatitis, and the prescribing information for the QW GLP-1RAs contains appropriate wording to highlight this risk.[11,12,16] The exact mechanisms by which GLP-1 RAs may increase the risk of acute pancreatitis are not known. Studies in mice show GLP-1 RA treatment results in an increase in acinar cell mass in the pancreas, which may enhance acinar cell protein synthesis including amylase and lipase.[55,56] Due to this potential risk, pancreatitis and pancreatic enzymes in GLP-1 RA Phase 3 clinical trials were monitored. GLP-1 RA treatment did not appear to substantially increase pancreatic events; the proportion of patients experiencing pancreatitis was low across all trials (≤1%) (Table 3). There were very few adjudication committee-confirmed events of pancreatitis; participants usually discontinued treatment and symptoms resolved within the duration of the trial.[26,31,35,41]

Confirmed events of acute pancreatitis were uncommon in the placebo-controlled CVOTs REWIND, EXSCEL and SUSTAIN 6.[21-23] Of note, these trials enrolled a larger number of patients and had longer follow-up times compared to the non-CVOT glycaemic

TABLE 3 Hypoglycaemia, injection-site events/reactions, pancreatic events, neoplasms and gallbladder events in QW GLP-1 RA Phase 3 trials

			Patients, n (%); events, n (if available)					
Trial	**Treatment arms**	**Number of patients**	**Hypoglycaemia (%)**	**Severe hypoglycaemia[a]**	**Injection-site events/ reactions[b]**	**Pancreatitis events**	**Neoplasms**	**Gallbladder events**
Dulaglutide trials								
[c]AWARD-1[39]	Dulaglutide QW 1.5 mg	279	10.4**	0	1 (<1)	1 (<1); 1	1 (<1)	NR
	Dulaglutide QW 0.75 mg	280	10.7	0	0	0	0	
	Exenatide BID 10 μg	276	15.9	2 events reported	1	0	0	
[c]AWARD-2[28]	Dulaglutide QW 1.5 mg	273	55.3*	2 (0.7)	2 (<1)	2 (<1); 2	NR	NR
	Dulaglutide QW 0.75 mg	272	54.4***	0	2 (<1)	1 (<1); 1		
	Insulin glargine QD	262	69.1	2 (0.8)	0	0		
AWARD-3[33]	Dulaglutide QW 1.5 mg	269	12.3	0	10 (3.7)	0	0 PC	NR
	Dulaglutide QW 0.75 mg	270	11.1	0	6 (2.2)	0	0 PC	
	Metformin QD 2000 mg	268	12.7	0	4 (1.5)	0	0 PC	
[c,d]AWARD-4[29]	Dulaglutide QW 1.5 mg	295	85.9	10 (3.4)	1 (<1)	0	0 PC, TC	NR
	Dulaglutide OW 0.75 mg	293	88.4	7 (2.4)	4 (1)	0	0 PC, TC	
	Insulin glargine QD	296	89.5	15 (5.1)	0	0	0 PC, TC	
[c]AWARD-5[35]	Dulaglutide QW 1.5 mg	304	10.2	0	0	0	0 TC	NR
	Dulaglutide QW 0.75 mg	302	5.3	0	0	0	0 TC	
	Sitagliptin QD 100 mg	315	4.8	0	NR	2 (<1); 2	0 TC	
	Placebo	177	NR	NR	NR	1 (<1)	0 TC	
[c]AWARD-6[40]	Dulaglutide QW 1.5 mg	299	9	0	1 (<1)	0	0 PC	NR
	Liraglutide QD 1.8 mg	300	6	0	2 (<1)	0	0 PC	
[d]AWARD-7[30]	Dulaglutide QW 1.5 mg	192	2**	0**	0	2 (1)	0	NR
	Dulaglutide QW 0.75mg	190	5	5 (3)	2 (1)	0 (0)	0	
	Insulin glargine QD	194	8	13 (7)	0	1 (1)	0	
[e]AWARD-8[47]	Dulaglutide QW 1.5 mg	239	20.9***	0	0	0	NR	NR
	Placebo	60	3.3***	0	0	0		
[d]AWARD-9[46]	Dulaglutide QW 1.5 mg	150	54.7	1 (0.7)	1 (<1)	0	0 PC, TC	NR
	Placebo	150	50.7	0	0	0	0 PC, TC	
[c]AWARD-10[48]	Dulaglutide QW 1.5 mg	142	4	0	1 (<1)	0	0 PC, TC	0
	Dulaglutide QW 0.75 mg	141	4	1 (0.7)	0	0	0 PC, TC	0
	Placebo	140	3	0	0	0	0 PC, TC	0

(Continues)

TABLE 3 (Continued)

Trial	Treatment arms	Number of patients	Patients, n (%); events, n (if available)					
			Hypoglycaemia (%)	Severe hypoglycaemia[a]	Injection-site events/ reactions[b]	Pancreatitis events	Neoplasms	Gallbladder events
REWIND[21]	Dulaglutide QW 1.5 mg	4949	NR	64 (1.3)	NR	23 (0.5)	[f]351 (7)	NR
	Placebo	4952		74 (1.5)		13 (0.3)	348 (7)	
Exenatide trials								
[e]DURATION-1[24]	Exenatide QW 2 mg	148	14.5	0[a]	26 (17.6)/7 (4.7)/1	0	NR	NR
	Exenatide BID 10 μg	145	16.5	0[a]	2 (1.4)/15 (10.3)/0 (pruritus/bruising/nodule)	0		
[c]DURATION-2[36]	Exenatide QW 2 mg	160	1	0[a]	16 (10); 28	0	0	0
	Sitagliptin QD 100 mg	166	3	0[a]	22 (7); 42 (sitagliptin and pioglitazone combined)	0	1 (<1)	0
	Pioglitazone QD 45 mg	165	1	0[a]		2 (1); 2	0	1(<1); 1
[c,e]DURATION-3[31]	Exenatide QW 2 mg	233	8[g]	1 (0.4)[a]	30 (13)	1 (<1)	NR	NR
	Insulin glargine QD	223	26[g]	2 (0.9)[a]	4 (2)	0		
DURATION-4[34]	Exenatide QW 2 mg	248	5.2	0[a]	26 (10.5)	0	NR	NR
	Metformin QD 2000 mg	246	4.1	0[a]	25 (10.2)	0		
	Pioglitazone QD 45 mg	163	3.7	0[a]	6 (3.7)	0		
	Sitagliptin QD 100 mg	163	3.1	0[a]	11 (6.7)	1 (<1)		
[c,e]DURATION-5[26]	Exenatide QW 2 mg	129	3.9	0[a]	17 (13)	1 (<1); 1	0 TC	NR
	Exenatide BID 10 μg	123	3.3	0[a]	12 (10)	0	0 TC	
DURATION-6[41]	Exenatide QW 2 mg	461	19	0[a]	Nodules: 48 (10) Pruritus 15 (3) Erythema: 10 (2)	1 (<1)	1 (<1)	NR
	Liraglutide QD 1.8 mg	450	15	0[a]	Nodules: 5 (1) Pruritus 1 (<1) Erythema: 3 (<1)	0	0	
[c,d,e]DURATION-7[49]	Exenatide QW 2 mg	232	29.7	0[a]	18 (7.8)	1 (<1)	4 (1.7)	NR
	Placebo	231	29.0	0[a]	7 (3)	0	2 (0.9)	

(Continues)

TABLE 3 (Continued)

Trial	Treatment arms	Number of patients	Patients, n (%); events, n (if available)					
			Hypoglycaemia (%)	Severe hypoglycaemia[a]	Injection-site events/ reactions[b]	Pancreatitis events	Neoplasms	Gallbladder events
[c]DURATION-8[50]	Exenatide QW 2 mg + dapagliflozin QD 10 mg	231	3	0[a]	28 (12)	1 (<1)	0 BC, PC, TC	
	Exenatide QW 2 mg	230	1	0[a]	27 (12)	1 (<1)	0 BC, PC, TC	NR
	Dapagliflozin QD 10 mg	233	1	0[a]	16 (7)	0	0 BC, PC, TC	
EXSCEL[22]	Exenatide QW 2 mg	7356	NR	247 (3.4)[a]	249 (3.4)[h]	26 (0.4)	15 PC, 2 TC	NR
	Placebo	7396		219 (3.0)[a]	134 (1.8)[h]	22 (0.3)	16 PC, 1 TC	
Semaglutide trials								
SUSTAIN 1[42]	Semaglutide QW 1 mg	130	NR	0 (0)[a]	NR	0	5 (4)	3 (2); 3
	Semaglutide QW 0.5 mg	128		0 (0)[a]		0	4 (4)	1 (1); 1
	Placebo	129		2 (2)[a]		0	0	0
SUSTAIN 2[37]	Semaglutide QW 1 mg	409	<1	0	NR	1 (<1); 1	10 (2); 11	7 (2); 7
	Semaglutide QW 0.5 mg	409	2	0		3 (1); 3	4 (1); 4	1 (<1); 1
	Sitagliptin QD 100 mg	407	1	2 (<1)		0	11 (3); 13	6 (1); 6
[c,e]SUSTAIN 3[43]	Semaglutide QW 1 mg	404	NR	33 (8.2)[a]	5 (1.2)	2 (<1)	15	6 (1.5)
	Exenatide QW 2 mg	405		33 (8.1)[a]	89 (22)	3 (<1)	8	2 (<1)
[c,d,e]SUSTAIN 4[32]	Semaglutide QW 1 mg	360	NR	5 (1)	NR	0	2 (1); 2	2 (1);2
	Semaglutide QW 0.5 mg	362		2 (<1)		2 (1); 2	8 (2); 9	1 (<1);1
	Insulin glargine QD	360		5 (1)		0	3 (1); 4	0
SUSTAIN 5[44]	Semaglutide QW 1 mg	131	NR	14 (10.7)[a]	NR	0	0	1 (<1); 1
	Semaglutide QW 0.5 mg	132		11 (8.3)[a]		0	4 (3.0); 5	3 (2.3); 3
	Placebo 1 mg or 0.5 mg	133		7 (5.3)[a]		0	1(<1); 1	0
[d]SUSTAIN 6[23]	Semaglutide QW 1 mg	822	NR	178 (21.7)[a]	9 (1.1)	3 (<1)	89 (10.8)	26 (3.2)
	Semaglutide QW 0.5 mg	826		191 (23.1)[a]	8 (1.0)	6 (<1)	66 (8)	32 (3.9)
	Placebo 1 mg	825		173 (21.0)[a]	12 (1.5)	9 (1)	69 (8.4)	23 (2.8)
	Placebo 0.5 mg	824		177 (21.5)[a]	9 (1.1)	3 (<1)	70 (8.5)	38 (4.6)
[c]SUSTAIN 7[45]	Semaglutide QW 1 mg	300	NR	5 (2)[a]	6 (2); 6	0	3 (1)	4 (1); 5
	Semaglutide QW 0.5 mg	301		2 (1)[a]	4 (1); 5	0	3 (1)	2 (1); 2
	Dulaglutide QW 1.5 mg	299		5 (2)[a]	8 (3); 17	0	3 (1)	8 (3); 9
	Dulaglutide QW 0.75 mg	299		3 (1)[a]	4 (1); 9	0	1(<1)	4 (1); 4

(Continues)

TABLE 3 (Continued)

Trial	Treatment arms	Number of patients	Patients, n (%); events, n (if available)					
			Hypoglycaemia (%)	Severe hypoglycaemia[a]	Injection-site events/ reactions[b]	Pancreatitis events	Neoplasms	Gallbladder events
SUSTAIN 8[38]	Semaglutide QW 1 mg	392	14	1 (<1)	NR	NR	2 (1)	NR
	Canagliflozin QD 300 mg	394	8	0 (0)			4 (1)	
[e]SUSTAIN 9[51]	Semaglutide QW 1 mg	150	11.3	1 (NR)	NR	0	4 (2.7); 4	NR
	Placebo	151	2.0	0		0	4 (2.6); 5	
[c,e]SUSTAIN 10[52]	Semaglutide QW 1 mg	289	NR	0	NR	0	9 (3.1)	NR
	Liraglutide QD 1.5 mg	287		0		2 (0.7)	4 (1.4)	

Note: Results shown are for the primary endpoint time, with the exception of AWARD 7, which is reported for the final study duration.

Abbreviations: ADA, American Diabetes Association; BC, bladder cancer; BID, twice-daily; GLP-1 RA, glucagon-like peptide-1 receptor agonist; QD, once-daily; QW, once-weekly; NR, not reported; PC, pancreatic cancer; TC, thyroid cancer.

[a]Severe/major hypoglycaemia was reported differently across the trials. For the AWARD trials, this was as per ADA classification,[53,54] whereas in the DURATION and SUSTAIN trials, severe (ADA classification) and blood glucose-confirmed hypoglycaemia (defined as 3.1 mmol/L or 56 mg/dL) were more commonly reported (and this combination is indicated specifically within the table by this symbol).

[b]Injection-site reaction definitions varied across trials.

[c]Trials allowed background metformin treatment.

[d]Trials allowed background insulin treatment.

[e]Trials allowed background sulphonylurea treatment.

[f]Reported as any cancer rather than neoplasm.

[g]Hypoglycaemia data for DURATION-3 are only for minor (confirmed) hypoglycaemia; rates for total hypoglycaemia were not reported.

[h]Injection-site reaction rates reported are those leading to premature discontinuation.

*$P < .05$.

**$P \leq .01$.

***$P \leq .001$.

control trials, making them better able to detect infrequent AEs. Rates of pancreatitis were low (≤1%) and comparable between the GLP-1 RA and placebo arms (Table 3).

To further understand the risk of pancreatitis, many trials also monitored pancreatic enzyme levels. Most trials reported an increase in pancreatic enzyme levels (amylase and lipase), which were often within the normal range. Pancreatic enzymes were increased from baseline in patients randomized to dulaglutide in AWARD-1 to -6, -8, -9 and -10 trials.[39,40,46-48] AWARD-7 and REWIND did not report on pancreatic enzyme levels.[21,30] DURATION-3 reported an increase in pancreatic enzymes from baseline with exenatide ER and insulin glargine.[31] In DURATION-7, increased lipase or amylase was reported in <1% across both arms.[49] DURATION-4 reported no significant differences between the treatment arms,[34] and DURATION-5 reported substantial variability in pancreatic amylase and lipase during the trial.[26] Pancreatic enzymes were elevated in patients receiving semaglutide (SUSTAIN 8, 9 and 10 did not report levels in the primary publications) and were higher in the semaglutide vs comparator arms across the SUSTAIN trials.[23,32,37,42-45]

In the QW GLP-1 RA head-to-head trials, small numerical differences were reported across both trials, but no statistical results were reported.[43,45] The clinical significance of these small increases in pancreatic enzymes and subtle differences between agents is unlikely to play a role in clinical decision-making between GLP-1 RA products.

Of note, the low rate of pancreatitis in the QW GLP-1 RA trials reported here is reflected in the findings of retrospective observational studies, which did not find an association between GLP-1 RA use and acute pancreatitis.[57,58] Furthermore, two recent meta-analyses of randomized controlled trials (RCTs) found no evidence that QW GLP-1 RA treatment increases the risk of acute pancreatitis or pancreatic cancer.[59,60] Guidelines recommend GLP-1 RAs should be used cautiously (if at all) in patients with a history of pancreatitis (due to lack of clinical trial data), and treatment be discontinued if acute pancreatitis develops.[4]

3.6 | Neoplasms

Preclinical studies have suggested GLP-1 RAs may be associated with an increased risk of thyroid C-cell tumours in rodents.[11,12,16] Guidelines and the boxed warnings in the prescribing information for all three QW GLP-1RAs contraindicate these drugs in patients with a personal or family history of medullary thyroid carcinoma or those with multiple endocrine neoplasia syndrome type 2.[4,11,12,16] The number of patients experiencing neoplasms was generally low in all trials (Table 3). This, along with variations in data reported (ie some reported the presence/absence of: pancreatic cancer[22,39] and/or thyroid cancer/carcinoma only,[22,26,29,36] and malignant and/or benign neoplasms[23,32,37,38,42-45,52] or a combination of these),[21,22,31,34,49,50] limited any meaningful between-drug comparisons. Proportions of patients with neoplasms were similar among the groups, including placebo,[21,23,35,38,42,44,48,49,51,52] suggesting patient characteristics and background therapies may play a role in their development.

3.7 | Gallbladder disorders

Type 2 diabetes is associated with gallbladder disease, and additional comorbidities such as obesity and dyslipidaemia may increase the risk of cholecystitis and cholelithiasis.[61,62] GLP-1 RA treatment has been linked with an increase in gallbladder events.[63] In a recent meta-analysis evaluating >90 clinical trials, involving 17 232 patients taking a GLP-1 RA vs 14 872 taking a comparator, a small but significant increased risk of cholelithiasis was reported with GLP-1 RA treatment (141 vs 99 cases, GLP-1 RA vs comparator, respectively; hazard ratio: 1.3 [95% confidence interval: 1.01-1.68, $P = .041$]),[60] which is why it is important to understand the Phase 3 clinical trial data.

AWARD-10 was the only trial with dulaglutide that reported on gallbladder events – no cases of cholelithiasis were found with dulaglutide or placebo.[48] Only DURATION-2 and -6 reported gallbladder events for exenatide ER; one case of acute cholecystitis was reported in the exenatide ER arm in DURATION 6.[36,41] The majority of SUSTAIN trials reported gallbladder events, including cholelithiasis and acute cholecystitis. One or more patients treated with semaglutide had gallbladder events in SUSTAIN 1 to 7 (reported in <1%-5% of patients), and their incidence was not always dose-related.[23,32,37,42-45] SUSTAIN 6 reported that cholelithiasis occurred more frequently than cholecystitis.[23] SUSTAIN 6 also reported that a similar proportion of patients in the placebo and semaglutide groups experienced gallbladder disorders, suggesting its incidence may have been related to the nature of the population recruited to the trial.[23] In the other SUSTAIN trials, events were also reported in comparator GLP-1 RA treatments (exenatide and dulaglutide) and the dipeptidyl peptidase-4 inhibitor sitagliptin (Table 3).[37,43,45] In the QW head-to-head trials, events were slightly higher for semaglutide (1.5%) compared with exenatide (<1%) in SUSTAIN 3.[43] In SUSTAIN 7, dulaglutide 1.5 mg had a greater frequency of events (3%) reported than either of the semaglutide doses or the lower 0.75 mg dulaglutide dose (all 1%).[45]

The underlying mechanism of this AE is not understood and warrants further investigation. Due to the low rates of events, any potential differences between agents remain unclear.

3.8 | Other safety outcomes

Other safety outcomes reported across the trials include microvascular outcomes (such as diabetic retinopathy [DR] and nephropathy), macrovascular outcomes and death.

3.8.1 | DR and its complications

DR and its complications were either not assessed or not reported at increased risk in the majority of QW GLP-1 RA trials. DR or its

complications (DRC) were not assessed in any of the AWARD trials,[28-30,33,35,39,40,46-48] and was only assessed as a secondary microvascular composite outcome (DR or renal outcomes) in REWIND.[21] The trial reported eye events in 1.9% vs 1.5% in patients receiving dulaglutide and placebo, respectively.[21] No trials involving exenatide ER reported DR in the primary publications.[22,24,26,31,34,36,49,50] DRCs (defined as vitreous haemorrhage, the onset of diabetes-related blindness, and/or the need for treatment with retinal photocoagulation or intravitreal agents) were assessed in SUSTAIN 6, whereas SUSTAIN 8 and 10 reported DR AEs.[23,38,52] The proportion of patients reporting retinopathy events did not differ significantly between patients receiving semaglutide and canagliflozin in SUSTAIN 8, or semaglutide and liraglutide in SUSTAIN 10.[38,52] A higher proportion of patients treated with semaglutide compared with placebo in SUSTAIN 6 reported DRCs (3.0% vs 1.8%, respectively).[23] However, it should be noted that SUSTAIN 6 did not systematically assess DR.[23] Also, a post hoc analysis of SUSTAIN 1-5 (and the Japanese SUSTAIN trials) showed no imbalance between semaglutide and its comparator arms for DR AEs.[64] It is known that rapid reductions in glycated haemoglobin (HbA_{1c}) are associated with an early worsening of DR,[65] and it has been suggested that the imbalance in retinopathy complications in SUSTAIN 6 was due to the rapid improvement in glucose control in patients with pre-existing DR.[64] The ADA guidelines recommend that all people with T2D should have an eye examination every 1-2 years, and once there are signs of DR, such eye exams should be at least annual.[66]

3.8.2 | Nephropathy

There is evidence to suggest that treatment with some GLP-1 RAs may reduce renal disease progression in patients with T2D.[67,68] However, from a safety perspective, there have been post-marketing reports of acute kidney injury and worsening of chronic renal failure with exenatide ER use.[12] DURATION-3 did not report on nephropathy specifically, but did report renal measurements (urinary albumin-to-creatinine ratio); however, no significant differences were observed between patients treated with exenatide ER and insulin glargine.[31] DURATION-8 reported an initial drop in estimated glomerular filtration rate (eGFR) levels followed by stabilization to baseline levels with exenatide ER.[50] From the trials that have completed more recently, acute renal failure was reported in four (1%) of the patients receiving semaglutide in SUSTAIN 8.[38]

All three labels for the QW GLP-1 RAs recommend that renal function is measured in patients with renal impairment who experience severe GI AEs during treatment, as these may worsen existing kidney problems.[11,12,16] With QW semaglutide and dulaglutide in patients with renal impairment, no dose adjustment is recommended.[11,16] Exenatide ER is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease.[12]

3.8.3 | Macrovascular

Type 2 diabetes is associated with macrovascular complications, with dyslipidaemia and elevated blood pressure being associated with an increased risk of CVD in patients with T2D.[4] The GLP-1 RA CVOTs SUSTAIN 6 and REWIND have shown CV benefit in patients with T2D, with or without CVD or at high risk of CVD, treated with dulaglutide and semaglutide.[21,23] The CVOT EXSCEL demonstrated non-inferiority, but not superiority, of exenatide ER to standard-of-care placebo.[22]

Dulaglutide appeared to have little effect on lipid profiles, although a small reduction of low-density lipoprotein cholesterol was reported in AWARD-2 (0.75 mg dose vs insulin glargine),[28] and improvements in high-density lipoprotein cholesterol were reported in AWARD-4 (both doses vs glargine).[29] Improvements were generally seen in lipid profiles in the majority of the trials with exenatide[22,24,26,31,34,36,49,50] and semaglutide.[32,37,38,42,43,51] Reductions were also reported in the four dulaglutide trials that measured lipid profiles (AWARD-1, -2, -5, and REWIND).[21,28,33,35] Systolic blood pressure decreased in the majority of trials,[21-24,26,29-34,36-38,40,42,44-51] but was only significantly reduced in some trials.[35,36,51]

A number of large epidemiological studies have linked elevated resting heart rate to increased CV risk,[69] and increased heart rate is a known GLP-1 RA class effect.[70] No harmful effect of this increase in heart rate has been reported with any of the GLP-1 RAs to date. Furthermore, an increase in heart rate was not reported to increase CV risk in patients with T2D and CVD (or at high risk of CVD) in two other major QD/BID GLP-1 RA CVOTs, ELIXA and LEADER.[67,68] Heart rate was not reported in AWARD-7[30] and DURATION-1, -2, and -6,[24,36,50] and was found to be increased in all other trials, ranging from an increase of 0.6[31] to 4.1 beats per minute.[28] The effect was more pronounced in QW vs QD GLP-1 RAs.[40,41]

3.9 | Death

Overall, mortality, where reported in the QW GLP-1 RA trials, was low, ranging from 0% to 1% in the AWARD and DURATION trials,[28,31,33,34,40,46,48] and from 0% to 4% in the SUSTAIN trials.[23,32,37,38,42,43,45] Mortality was higher in the REWIND trial, likely due to the eligibility criteria and trial duration, but comparable across the dulaglutide and placebo arms (11% vs 12%).[21]

3.10 | Special populations

All prescribing information for the QW GLP-1 RAs include a section on use in specific populations such as patients with renal impairment, elderly, paediatric patients and pregnant women; however, clinical data on the use of GLP-1 RAs in these populations are lacking.[11,12,16]

QW GLP-1 RA trials specifically evaluating patients with severe renal impairment or chronic kidney disease (CKD) are limited. A renal benefit was seen in patients treated with dulaglutide in

the AWARD-7 trial, which enrolled patients with T2D and moderate-to-severe CKD (stages 3-4), and the product label has been updated to reflect this.[11,30] Specifically, the renal benefit involved a significantly smaller decline in eGFR, and albuminuria was reduced compared with insulin glargine.[30]

Treatment with QW GLP-1 RAs in elderly patients has shown beneficial outcomes[71]; however, caution should be exercised in frail, elderly patients due to the GI effects and potential body weight loss associated with this drug class.[66] In a pooled analysis of SUSTAIN 1-5, similar proportions of elderly (≥65 years old) and non-elderly patients (<65 years old) experienced AEs. However, more elderly patients prematurely discontinued treatment due to increased GI AEs compared with non-elderly patients.[71] Moreover, elderly patients had higher incidences of neoplasms, CV events and pancreatitis compared with non-elderly patients.[71]

Data on the use of QW GLP-1 RAs in paediatric patients are also lacking. Liraglutide is currently the only GLP-1 RA approved in paediatric patients following results from the ellipse trial, but use is QD.[14,72] Incidence of GI AEs in the ellipse trial was as expected for this drug class, and a higher proportion of patients experienced serious AEs and hypoglycaemic episodes vs placebo.[72] There is a trial underway with QW exenatide ER in paediatric patients with T2D.[73]

There are no clinical trials investigating QW GLP-1 RAs in pregnant women and they are not currently recommended in pregnancy, unless the benefits outweigh the risks, and for semaglutide, it is recommended that women planning a pregnancy should discontinue use at least 2 months prior to trying to conceive.[11,12,16]

4 | DISCUSSION

The QW GLP-1 RAs are relatively new additions to the T2D treatment armamentarium, though QD GLP-1 RAs have been in use since 2005.[6] Only two trials involving direct QW GLP-1 RAs head-to-head comparisons were identified in this review, limiting direct comparison of safety and tolerability. The remaining head-to-head trials compared QW vs QD or BID formulations.

The most commonly reported AEs were GI disorders (nausea, vomiting and diarrhoea), but frequencies differed between the three QW GLP-1 RAs. The issue of GI tolerability may affect patient adherence; however, these effects appear to be mostly mild-to-moderate in severity, reduce over time, and a slow up-titration schedule may help to alleviate or prevent nausea.[74] Nausea, vomiting and diarrhoea can also present with gastroparesis or severe gastroesophageal reflux disease, and guidelines recommend careful monitoring of patients with these conditions when using GLP-1 RAs.[4]

Aside from the GI AEs, other safety concerns include hypoglycaemia, ISRs, neoplasms, gallbladder events and microvascular and macrovascular outcomes. Risk of hypoglycaemia and ISRs, pancreatic events and neoplasms was generally low across the GLP-1 RAs. There is evidence to suggest an association of GLP-1 RAs with gallbladder AEs;[63] however, rates of gallbladder disorders were low across the trials. In the direct QW head-to-head trials, rates were more frequent with semaglutide than exenatide ER in SUSTAIN 3,[43] but lower with semaglutide 0.5 and 1 mg than those reported with dulaglutide 1.5 mg in SUSTAIN 7.[45] The majority of trials did not report on DR,[22,24,26,28-31,33-36,39,40,46-50] and renal outcomes were only reported in SUSTAIN 6 and REWIND.[21,23] A recent meta-analysis of 60 studies evaluating microvascular outcomes in patients with T2D concluded that treatment with GLP-1 RAs did not increase the incidence of DR and was safe regarding progression of albuminuria.[75] With respect to risk factors of macrovascular outcomes, QW GLP-1 RA treatment appeared to be associated with an increase in heart rate and reductions in lipids and blood pressure. It is unclear to what degree changes in these specific risk factors play a role in overall macrovascular outcomes, and the underlying mechanisms and clinical relevance have yet to be established. More important than the effects on surrogate markers are the results of the CVOTs, which demonstrate CV benefit with dulaglutide[21] and semaglutide,[23] and CV safety with exenatide ER.[22]

It is important for all HCPs to be aware of which special populations can and cannot be treated with QW GLP-1 RAs. Trials in special populations, such as patients with CKD, the elderly and paediatric populations, are limited and warrant further investigation. With the exception of exenatide, all QW GLP-1 RAs can be used without dose adjustments in patients with renal impairment[11,12,16]; specifically, dulaglutide and semaglutide can be used in patients with severe renal impairment without dose adjustment,[11,16] but exenatide should not.[12] Comorbidities and polypharmacy can potentially complicate T2D treatment in elderly populations. There are currently no published data for pregnant women.

This review has focused on data from Phase 3 RCTs, and though these are considered the 'gold standard' for evaluating drug safety and efficacy, they do not necessarily represent what is seen in the real-world practice setting. Patient populations in RCTs are often quite homogeneous and recruited using strict inclusion/exclusion criteria, making it difficult to determine whether these restrictions have an impact on the trial results. There is a need to collect real-world data in diverse and heterogeneous populations to complement the evidence of effectiveness seen in RCTs.

QW GLP-1 RAs use is likely to increase, given their positioning in guidelines.[3,4,10] Thus, pharmacists and HCPs need to be aware of the safety profiles of the available treatments to make informed decisions regarding the best treatment options for their patients. As well as considering the safety and tolerability when choosing a treatment for glycaemic control, a patient-centred approach needs to be adopted, the importance of which is emphasized in the ADA/European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists and American College of Endocrinology consensus statements.[3,4] The currently available QW GLP-1 RAs have proven efficacy,[3] with favourable safety and tolerability profiles. Additional head-to-head trials with different or new comparators will help to further understand the differences in safety and tolerability within this drug class. With respect to QW GLP-1 RAs not yet on the market, two novel drugs are currently in late clinical stage of development. Tirzepatide is a dual GLP-1 receptor/

glucose-dependent insulinotropic polypeptide agonist, which has already demonstrated glucose lowering and weight reductions in a Phase 2b trial.[76] The safety profile for tirzepatide is similar to that reported for other GLP-1 RAs, with most AEs being GI-related; however, the rates would appear higher with tirzepatide than existing medications.[76] Meanwhile, efpeglenatide is being investigated head-to-head against dulaglutide in a 56-week, randomized, open-label, Phase 3 trial, AMPLITUDE-D.[77]

5 | WHAT IS NEW AND CONCLUSION

This comprehensive safety and tolerability overview of the currently approved and marketed QW GLP-1 RAs puts newly published clinical trial results into the context of older Phase 3 trials. In the growing market of T2D treatments, pharmacists and HCPs need an overview of GLP-1 RA safety and tolerability, allowing them to have informed discussions on the suitability of long-term treatment strategies with patients. This review highlights the areas of interest for such HCPs and provides them with the detailed data that allow them to inform patients on the most common side effects of GLP-1 RA treatment.

Direct safety and tolerability comparisons cannot be made between the QW GLP-1 RAs as only a limited number of direct head-to-head studies have been undertaken. The favourable safety and tolerability profiles of QW GLP-1 RAs, in combination with their efficacy, make them attractive treatment options for patients with T2D. There are some differences within the class, with respect to GI, macrovascular and microvascular outcomes, and these should be considered when choosing the optimal treatment for patients.

ACKNOWLEDGEMENTS

The author is grateful to Aneela Majid, PhD, of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc, for writing assistance. This assistance was funded by Novo Nordisk Inc., which also reviewed the manuscript for scientific accuracy.

CONFLICT OF INTEREST

J Trujillo has acted as a consultant and advisory board member for Novo Nordisk, Sanofi and BD Pharmaceuticals.

ORCID

Jennifer Trujillo https://orcid.org/0000-0001-7898-8029

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1789–1858.
2. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet*. 2014;383:1068-1083.
3. Buse JB, Wexler DJ, Tsapas A, et al. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;2020(43):487-493.
4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2019 executive summary. *Endocr Pract*. 2019;25:69-100.
5. Cannon A, Handelsman Y, Heile M, Shannon M. Burden of Illness in Type 2 Diabetes Mellitus. *J Manag Care Spec Pharm*. 2018;24:S5-S13.
6. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2009;5:262-269.
7. Nauck MA, Vilsbøll T, Gallwitz B, Garber A, Madsbad S. Incretin-based therapies: viewpoints on the way to consensus. *Diabetes Care*. 2009;32(Suppl 2):S223-S231.
8. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19:524-536.
9. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014;384:2228-2234.
10. European Society of Cardiology. 2019 ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2019;00:1-69.
11. Eli Lilly and Company. Trulicity (dulaglutide) injection for subcutaneous use; prescribing information. 2020. https://pi.lilly.com/us/trulicity-uspi.pdf. Accessed April 17, 2020.
12. Amylin Pharmaceuticals. Bydureon® (exenatide extended-release) for injectable suspension, for subcutaneous use prescribing information. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022200s026lbl.pdf. Accessed May 17, 2019.
13. Amylin Pharmaceuticals. Byetta® (exenatide) injection, prescribing information. 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf. Accessed February 28, 2018.
14. Novo Nordisk A/S. Victoza® (liraglutide), prescribing information. 2019. https://www.novo-pi.com/victoza.pdf. Accessed July 27, 2019.
15. Sanofi-Aventis US. Adlyxin (lixisenatide), prescribing information. 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471Orig1s000lbl.pdf. Accessed February 28, 2018.
16. Novo Nordisk A/S. Ozempic (semaglutide) injection, for subcutaneous use; prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209637s003lbl.pdf. Accessed January 28, 2020.
17. Novo Nordisk A/S. Rybelsus (semaglutide) tablets, for oral use; Prescribing information. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf. Accessed September 27, 2019.
18. Andersen A, Lund A, Knop FK, Vilsboll T. Glucagon-like peptide 1 in health and disease. *Nat Rev Endocrinol*. 2018;14:390-403.
19. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab*. 2016;18:317-332.
20. GlaxoSmithKline. Tanzeum (albiglutide) discontinuation. 2017. https://www.tanzeum.com/pdfs/consumer-faq.pdf. Accessed February 28, 2018.
21. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121-130.
22. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228-1239.

23. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834-1844.
24. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372:1240-1250.
25. ClinicalTrials.gov. Effects of exenatide long-acting release on glucose control and safety in subjects with type 2 diabetes mellitus (Duration-1). 2015. https://clinicaltrials.gov/ct2/show/study/NCT00308139. Accessed June 26, 2019.
26. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:1301-1310.
27. Sun F, Chai S, Yu K, et al. Gastrointestinal adverse events of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Technol Ther*. 2015;17:35-42.
28. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care*. 2015;38:2241-2249.
29. Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet*. 2015;385:2057-2066.
30. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6:605-617.
31. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet*. 2010;375:2234-2243.
32. Aroda VR, Bain SC, Cariou B, 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;5:355-366.
33. Umpierrez G, Tofe Povedano S, Perez Manghi F, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care*. 2014;37:2168-2176.
34. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care*. 2012;35:252-258.
35. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37:2149-2158.
36. Bergenstal RM, Wysham C, Macconell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet*. 2010;376:431-439.
37. Ahren B, Masmiquel L, Kumar H, 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;5:341-354.
38. Lingvay I, Catarig AM, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:834-844.
39. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*. 2014;37:2159-2167.
40. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384:1349-1357.
41. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381:117-124.
42. Sorli C, Harashima S-I, Tsoukas GM, 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;5:251-260.
43. Ahmann AJ, Capehorn M, Charpentier G, 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;41:258-266.
44. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomised, controlled trial. *J Clin Endocrinol Metab*. 2018;103:2291-2301.
45. Pratley RE, Aroda VR, Lingvay I, 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*:275-286.
46. Pozzilli P, Norwood P, Jodar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). *Diabetes Obes Metab*. 2017;19:1024-1031.
47. Dungan KM, Weitgasser R, Perez Manghi F, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). *Diabetes Obes Metab*. 2016;18:475-482.
48. Ludvik B, Frias JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6:370-381.
49. Guja C, Frias JP, Somogyi A, et al. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study. *Diabetes Obes Metab*. 2018;20:1602-1614.
50. Frias JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:1004-1016.
51. Zinman B, Bhosekar V, Busch R, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:356-367.
52. Capehorn M, Janez A, Price H, et al. Efficacy and safety of semaglutide 1.0 mg once weekly vs liraglutide 1.2mg once daily as add-on to 1–3 oral antidiabetic drugs in subjects with Type 2 diabetes (SUSTAIN 10). *Diabet Metab*. 2019. 10.1016/j.diabet.2019.101117.
53. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care*. 2005;28:1245-1249.

54. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab*. 2013;98:1845-1859.
55. Koehler JA, Baggio LL, Cao X, et al. Glucagon-like peptide-1 receptor agonists increase pancreatic mass by induction of protein synthesis. *Diabetes*. 2015;64:1046-1056.
56. Hou Y, Ernst SA, Heidenreich K, Williams JA. Glucagon-like peptide-1 receptor is present in pancreatic acinar cells and regulates amylase secretion through cAMP. *Am J Physiol Gastrointest Liver Physiol*. 2016;310:G26-33.
57. Giorda CB, Sacerdote C, Nada E, Marafetti L, Baldi I, Gnavi R. Incretin-based therapies and acute pancreatitis risk: a systematic review and meta-analysis of observational studies. *Endocrine*. 2015;48:461-471.
58. Wang T, Wang F, Gou Z, et al. Using real-world data to evaluate the association of incretin-based therapies with risk of acute pancreatitis: a meta-analysis of 1,324,515 patients from observational studies. *Diabetes Obes Metab*. 2015;17:32-41.
59. Storgaard H, Cold F, Gluud LL, Vilsbøll T, Knop FK. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19:906-908.
60. Monami M, Nreu B, Scatena A, et al. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): Data from randomized controlled trials. *Diabetes Obes Metab*. 2017;19:1233-1241.
61. Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care*. 2009;32:834-838.
62. Pagliarulo M, Fornari F, Fraquelli M, et al. Gallstone disease and related risk factors in a large cohort of diabetic patients. *Dig Liver Dis*. 2004;36:130-134.
63. Pizzimenti V, Giandalia A, Cucinotta D, et al. Incretin-based therapy and acute cholecystitis: a review of case reports and EudraVigilance spontaneous adverse drug reaction reporting database. *J Clin Pharm Ther*. 2016;41:116-118.
64. Vilsbøll T, Bain SC, Leiter LA, et al. Semaglutide, reduction in HbA1c and the risk of diabetic retinopathy. *Diabetes Obes Metab*. 2018. https://doi.org/10.1111/dom.13172
65. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the diabetes control and complications trial. *Arch Ophthalmol*. 1998;116:874-886.
66. American Diabetes Association. Standards of medical care in diabetes – 2020. *Diabetes Care*. 2020;43:S1-S224.
67. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.
68. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247-2257.
69. Arnold JM, Fitchett DH, Howlett JG, Lonn EM, Tardif JC. Resting heart rate: a modifiable prognostic indicator of cardiovascular risk and outcomes? *Can J Cardiol*. 2008;24:3A–15A.
70. Lorenz M, Lawson F, Owens D, et al. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. *Cardiovasc Diabetol*. 2017;16:6.
71. 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;20:2291-2297.
72. Tamborlane WV, Barrientos-Perez M, Fainberg U, et al. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med*. 2019;381:637-646.
73. ClinicalTrials.gov. Safety and efficacy study of exenatide once weekly in adolescents with type 2 diabetes. 2019. https://clinicaltrials.gov/ct2/show/NCT01554618. Accessed July 15, 2019.
74. Lingvay I, Leiter LA. Use of GLP-1 RAs in cardiovascular disease prevention: a practical guide. *Circulation*. 2018;137:2200-2202.
75. Avgerinos I, Karagiannis T, Malandris K, et al. Glucagon-like peptide-1 receptor agonists and microvascular outcomes in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2019;21:188-193.
76. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392:2180-2193.
77. ClinicalTrials.gov. Efficacy and safety of efpeglenatide versus dulaglutide in patients with type 2 diabetes mellitus inadequately controlled with metformin (AMPLITUDE-D). 2019. https://clinicaltrials.gov/ct2/show/record/NCT03684642. Accessed July 15, 2019.

How to cite this article: Trujillo J. Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes. *J Clin Pharm Ther*. 2020;45(Suppl 1):43–60. https://doi.org/10.1111/jcpt.13225