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REVIEW ARTICLE

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Glycaemic and non-glycaemic efficacy of once-weekly GLP-1 receptor agonists in people with type 2 diabetes

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Summary

What is known and objective: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may confer a range of benefits for people with type 2 diabetes (T2D), which is reflected through their position within diabetes treatment guidelines. The objective of this narrative review is to explore the efficacy data of once-weekly (QW) GLP-1 RAs in terms of glycaemic control, body weight reduction, cardiovascular (CV) outcomes and potential renal protective effects to assist pharmacists and other healthcare professionals (HCPs) in treatment discussions with patients.

Methods: This a narrative review focused on 31 clinical trials involving the Phase 3 clinical programmes of the QW GLP-1 RAs dulaglutide, exenatide extended-release (ER) and semaglutide subcutaneous (s.c.).

Results and discussion: The clinical trials were divided by their comparator arms and examined for trends. All QW GLP-1 RAs were superior to placebo for reductions in glycated haemoglobin (HbA_{1c}) and body weight. Data regarding QW GLP-1 RAs versus metformin were limited, likely due to metformin's use as the first-line pharmacologic for T2D. In the robust head-to-head trials of QW versus QW GLP-1 RAs, semaglutide s.c. was superior to both dulaglutide and exenatide ER regarding HbA_{1c} and body weight; however, QW versus once-daily GLP-1 RA trials had mixed results depending on the comparators. Finally, in QW GLP-1 RA versus insulin trials, all QW GLP-1 RAs were as effective as insulin, particularly when hypoglycaemia and body weight were also considered. CV outcome trials demonstrated benefits in major adverse CV events and renal outcomes for semaglutide and dulaglutide.

What is new and conclusion: This review collates recently published data and previously published Phase 3 results to allow pharmacists and other HCPs to understand all of the efficacy data available and the corresponding impact on treatment guidelines. QW GLP-1 RAs are emerging as important therapeutic options for people with T2D as they offer a spectrum of benefits extending beyond glycaemic control, but it is important to be aware of their efficacy differences when prescribing and discussing them with patients.

KEYWORDS
efficacy, glucagon-like peptide-1 receptor agonist, glycaemic control, type 2 diabetes, weight loss

1 | WHAT IS KNOWN AND OBJECTIVE

The incretin hormone glucagon-like peptide-1 (GLP-1) is secreted in response to the ingestion of food.[1] In a glucose-dependent manner, it amplifies the production and secretion of insulin and suppresses the release of glucagon, while also stimulating the growth of new beta-cells in the pancreas.[2,3] Through their insulinotropic and glucagonostatic effects, agonists for the GLP-1 receptor have been proven to be an effective approach to managing the glycaemic levels of people with type 2 diabetes (T2D).[2]

Similar to the endogenous hormone, GLP-1 receptor agonists (GLP-1 RAs) have other pleiotropic effects such as slowing gastric emptying and increasing satiety.[2,4] Consequently, the clinical use of GLP-1 RAs has been associated with weight loss and a reduction in major adverse cardiovascular events (MACE).[5-8] There is also growing evidence supporting a renoprotective effect conferred by GLP-1 RAs.[6,7,9] It is important for pharmacists and other healthcare professionals (HCPs) to be aware of each of these aspects as they discuss treatment options with patients.

The broad range of benefits offered by GLP-1 RAs is aligned with recent guideline recommendations, which emphasize an approach to the management of T2D that encompasses more than just glycaemic control.[10-13] Additionally, in people with T2D and atherosclerotic cardiovascular (CV) disease, GLP-1 RAs are recommended as the first line of antihyperglycaemic therapy by the European Society of Cardiology (ESC) and the first injectable antihyperglycaemic agent by the American Diabetes Association (ADA), the American College of Cardiology/American Heart Association (ACC/AHA) and the European Association for the Study of Diabetes (EASD).[10-12,14] It should be noted, however, that gastrointestinal (GI) problems (such as nausea and vomiting) are a common class side effect of GLP-1 RAs and therefore must be factored into prescribing decisions.[10]

Extensive effort has been invested in testing GLP-1 RA once-weekly (QW) subcutaneous (s.c.) injections (eg the AWARD, DURATION and SUSTAIN programmes[8,15,16]). A QW formulation has the potential to reduce the overall treatment burden of people managing T2D by lowering the number of injections required compared with once-daily (QD) and twice-daily (BID) GLP-1 RAs and may also delay the need for treatment intensification to basal or frequent prandial insulin injections in order to achieve adequate glycaemic control.[10,12] QW, compared with QD and BID GLP-1 RA formulations, has different pharmacodynamic and pharmacokinetic properties[17-22] that may impact their clinical profiles in terms of efficacy and tolerability.[4]

The objective of this narrative review is to help pharmacists and other HCPs to develop an awareness of the efficacy differences within the QW class of GLP-1 RAs, focusing on glycaemic control and, beyond it, on body weight reductions and other pleiotropic effects. Additionally, where possible and relevant, these more traditional efficacy results will be placed in the context of newer CV outcomes and potential renal benefits. Three QW GLP-1 RAs are commercially available at present: dulaglutide,[17] exenatide extended-release (ER)[20] and semaglutide.[21] A fourth, albiglutide,[23] was available until 2018, when it was withdrawn from the market for non-clinical, commercial reasons. Through analysing the data from QW GLP-1 RA Phase 3 trials used to support applications for approval to the US Food and Drug Administration and other longer-duration Phase 3 trials, this review will help pharmacists to understand these differences and explain them to people with T2D, in turn helping to optimize their treatment.

2 | METHODS

This is a narrative review focused primarily on data from Phase 3 clinical trials involving the QW GLP-1 RAs dulaglutide, exenatide ER and semaglutide s.c. PubMed was searched to ensure all relevant clinical trials were included, as were the bibliographies of the related primary publications and reviews discussing them. The trials were classified by comparator arms to align with steps within treatment guidelines.

3 | RESULTS AND DISCUSSION

3.1 | Source information

Data from 31 clinical trials have been included within this review: 11 pertaining to dulaglutide, 10 to exenatide ER and 10 to semaglutide (Table 1). These trials employed a variety of designs with different treatment backgrounds, populations and durations. This substantially limits the extent to which data can be compared across the trials and, as such, the only direct QW GLP-1 RA comparisons that are made in this review come from head-to-head trials involving two or more comparators on the same trial background.

3.2 | QW GLP-1 RAs versus placebo

There were 10 randomized trials of QW GLP-1 RAs that directly compared dulaglutide,[7,15,24,25] exenatide ER[26-28] or semaglutide[6,8,29] against placebo (Table 2). These ranged in duration from 24 weeks to 8 years (median follow-up time of 5.4 years) and, other than the CV outcome trials (CVOTs) REWIND, EXSCEL and SUSTAIN 6,[6,7,28] measured change from baseline in glycated haemoglobin (HbA_{1c}) as the primary endpoint. All 10 trials found statistically significant

TABLE 1 Key Phase 3 trials of QW GLP-1 RAs included in this review

Trial name	Study design	Treatment interventions	Study duration	Primary endpoint	Permitted concomitant treatments
DURATION-1[16]	Randomized, comparator-controlled, open-label	Exenatide ER	52 weeks	Change from baseline in HbA_{1c} at Week 52	SU
DURATION-2[70]	Randomized, double-blind	Exenatide ER, sitagliptin, pioglitazone	26 weeks	Change from baseline in HbA_{1c} at Week 26	Metformin, ± SU
DURATION-3[79]	Randomized, open-label	Exenatide ER	26 weeks	Change from baseline in HbA_{1c} at Week 26	Metformin, ± SU
DURATION-4[31]	Randomized, double-blind	Exenatide ER, metformin, pioglitazone, sitagliptin	26 weeks	Change from baseline in HbA_{1c} at Week 26	None
DURATION-5[37]	Randomized, open-label, comparator-controlled	Exenatide ER, exenatide (BID)	24 weeks	Change from baseline in HbA_{1c} at Week 24	Metformin, SU, TZD, or a combination of these
DURATION-6[38]	Open-label, randomized, parallel group	Exenatide ER, liraglutide (QD)	26 weeks	Change from baseline in HbA_{1c} at Week 26	Metformin, SU, metformin + SU, or metformin + pioglitazone
DURATION-7[27]	Randomized, double-blind, parallel group, placebo-controlled	Exenatide ER, placebo	28 weeks	Change from baseline HbA_{1c} at Week 28	Insulin glargine ± (metformin ± SU)
DURATION-8[59]	Randomized, double-blind, active-controlled	Exenatide ER, dapagliflozin, exenatide ER + dapagliflozin	28 weeks	Change from baseline in HbA_{1c} at Week 28	Metformin
DURATION-NEO-2[26]	Randomized, open-label, active- and placebo-controlled	Exenatide ER AI, sitagliptin, placebo	28 weeks	Change from baseline in HbA_{1c} at Week 28	Metformin
EXSCEL[28]	Randomized, double-blind, placebo-controlled	Exenatide ER, placebo	Event driven (median follow-up 3.2 years)	First occurrence of MACE in a time-to-event analysis	≤3 OADs, or ≤2 OADS + insulin
AWARD-1[15]	Randomized, blinded, parallel group and placebo-controlled	Dulaglutide, exenatide, placebo	52 weeks	Change from baseline in HbA_{1c} at Week 26	Pioglitazone and metformin
AWARD-2[78]	Randomized, open-label (double-blind to dulaglutide dose), comparator-controlled	Dulaglutide, insulin glargine	78 weeks	Change from baseline in HbA_{1c} at Week 52	Metformin and glimepiride
AWARD-3[30]	Randomized, double-blind, double-dummy, parallel group	Dulaglutide, metformin	52 weeks	Change from baseline in HbA_{1c} at Week 26	None
AWARD-4[50]	Randomized, open-label	Dulaglutide, insulin glargine	52 weeks	Change from baseline in HbA_{1c} at Week 26	Insulin lispro, with or without metformin
AWARD-5[69]	Randomized, double-blind, adaptive, parallel group	Dulaglutide, sitagliptin	52 weeks	Change from baseline in HbA_{1c} at Week 52	Metformin
AWARD-6[36]	Randomized, open-label	Dulaglutide, liraglutide	26 weeks	Change from baseline in HbA_{1c} at Week 26	Metformin
AWARD-7[9]	Open-label, randomized, parallel group	Dulaglutide, insulin glargine	52 weeks	Change from baseline in HbA_{1c} at Week 26	Insulin lispro

(Continues)

TABLE 1 (Continued)

Trial name	Study design	Treatment interventions	Study duration	Primary endpoint	Permitted concomitant treatments
AWARD-8[24]	Randomized, double-blind, placebo-controlled, parallel group	Dulaglutide, placebo	24 weeks	Change from baseline in HbA_{1c} at Week 24	Glimepiride
AWARD-9[25]	Randomized, double-blind, placebo-controlled, parallel group	Dulaglutide, placebo	28 weeks	Change from baseline in HbA_{1c} at Week 28	Insulin glargine ± metformin
AWARD-10[54]	Randomized, double-blind, placebo-controlled, parallel group	Dulaglutide, placebo	24 weeks	Change from baseline in HbA_{1c} at Week 24	SGLT2is ± metformin
REWIND[7]	Randomized, double-blind, placebo-controlled	Dulaglutide, placebo	Event driven, follow-up of up to 8 years (median follow-up 5.4 years)	First occurrence of MACE	Antihyperglycaemic therapies excluding DPP4is or GLP-1 RAs
SUSTAIN 1[8]	Randomized, double-blind, parallel group	Semaglutide s.c., placebo	30 weeks	Change from baseline in HbA_{1c} at Week 30	Metformin, OADs excluding GLP-1 RAs or DDP4is
SUSTAIN 2[71]	Randomized, double-blind, double-dummy, active-controlled, parallel group	Semaglutide s.c., sitagliptin	56 weeks	Change from baseline in HbA_{1c} at Week 56	Metformin, TZDs, Metformin + TZDs
SUSTAIN 3[39]	Randomized, open-label, active comparator-controlled, parallel group	Semaglutide s.c., exenatide ER	56 weeks	Change from baseline in HbA_{1c} at Week 56	Metformin ± TZDs/SUs
SUSTAIN 4[80]	Randomized, open-label, active-controlled, parallel group	Semaglutide s.c., insulin glargine	30 weeks	Change from baseline in HbA_{1c} at Week 30	Metformin, SU
SUSTAIN 5[29]	Randomized, double-blind, placebo-controlled, parallel group	Semaglutide s.c., placebo	30 weeks	Change from baseline in HbA_{1c} at Week 30	Basal insulin ± metformin
SUSTAIN 6[6]	Randomized, double-blind, placebo-controlled, parallel group	Semaglutide s.c., placebo	Event driven, Median follow-up of 2.1 years	First occurrence of MACE over 2.1 years	≤2 OADs ± basal or premixed insulin (no incretin-based medications were allowed)
SUSTAIN 7[40]	Randomized, open-label, active-controlled, parallel group	Semaglutide s.c., dulaglutide	40 weeks	Change from baseline in HbA_{1c} at Week 40	Metformin
SUSTAIN 8	Randomized, double-blind comparator-controlled parallel group	Semaglutide s.c., canagliflozin	52 weeks	Change from baseline in HbA_{1c} at Week 52	Metformin
SUSTAIN 9[55]	Randomized, placebo-controlled, double-blind, parallel group	Semaglutide s.c., placebo	30 weeks	Change from baseline in HbA_{1c} at Week 30	Metformin, SGLT2is, SUs
SUSTAIN 10[35]	Randomized, open-label	Semaglutide s.c., liraglutide	30 weeks	Change from baseline in HbA_{1c} at Week 30	1–3 OADs

Abbreviations: BID, twice-daily; DPP4i, dipeptidyl peptidase-4 inhibitor; exenatide ER, exenatide extended-release; exenatide ER AI, exenatide ER auto-injectable; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; MACE, major cardiovascular adverse events; OAD, oral anti-diabetic; QD, once-daily; QW, once-weekly; s.c., subcutaneous; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

TABLE 2 HbA_{1c} and body weight change from trials that compared QW GLP-1 RAs with placebo

Trial name, time until primary endpoint	Treatment arms	Permitted concomitant treatments	ETD HbA_{1c}, % [95% CI]; *P*-value (vs placebo)	ETD body weight, kg [95% CI]; *P*-value (vs placebo)
AWARD-1[15], 26 weeks	Dulaglutide 0.75 mg	Metformin and/or pioglitazone	−0.84 [−1.01; −0.67]; <.001	1.27 [95% CI: NR]; <.001[a]
	Dulaglutide 1.5 mg		−1.05 [−1.22; −0.88]; <.001	−0.24 [95% CI: NR]; .474[a]
	Exenatide BID 10 μg			
	Placebo			
AWARD-8[24], 24 weeks	Dulaglutide 1.5 mg	Glimepiride	−1.3 [−1.6; −1.0]; <.001	−0.68 [−1.53; 0.18]; NS
	Placebo			
AWARD-9[25], 28 weeks	Dulaglutide 1.5 mg	Insulin glargine ± metformin	−0.77 [−0.97; −0.56]; <.001	−2.41 [−3.19; −1.64]; <.001
	Placebo			
REWIND[7] (median follow-up 5.4 years)	Dulaglutide 1.5 mg	Antihyperglycaemics except DPP4is or GLP-1 RAs	−0.61 [−0.65; −0.58]; <.0001 (at 5 months' follow-up)	−1.46 [−1.67; −1.25]; <.0001 (at 5 months' follow-up)
	Placebo			
DURATION-NEO-2[26], 28 weeks	Exenatide ER AI 2 mg	Metformin	−0.72 [−1.15; −0.30]; .001	−1.3 [−2.3; −0.2]; .020
	Placebo			
DURATION-7[27], 28 weeks	Exenatide ER 2 mg	Metformin ± insulin glargine	−0.7 [−0.9; −0.5]; <.001	−1.5 [−2.1; −0.8]; <.001
	Placebo			
EXSCEL[28] (median follow-up 3.2 years)	Exenatide ER 2 mg	Non-incretin-based therapies	−0.53 [−0.57; −0.50]; <.001	−1.27 [−1.40; −1.13]; <.001
	Placebo			
SUSTAIN 1[8], 30 weeks	Semaglutide s.c. 0.5 mg	Metformin, OADs (excluding GLP-1 RAs or DDP4is)	−1.43 [−1.71; −1.51]; <.0001	−2.75 [−3.92; −1.58]; <.0001
	Semaglutide s.c. 1 mg		−1.53 [−1.81; −1.25]; <.0001	−3.56 [−4.74; −2.38]; <.0001
	Placebo			
SUSTAIN 5[29], 30 weeks	Semaglutide s.c. 0.5 mg	Basal insulin ± metformin	−1.35 [−1.61; −1.50]; <.0001	−2.31 [−3.33; −1.29]; <.0001
	Semaglutide s.c. 1 mg		−1.75 [−2.01; −1.50]; <.0001	−5.06 [−6.08; −4.04]; <.0001
	Placebo			
SUSTAIN 6[6] (median follow-up 2.1 years)	Semaglutide s.c. 0.5 mg	Non-incretin-based therapies	−0.66 [−0.80; −0.52]; .0001	−2.87 [−3.47; −2.28]; <.0001
	Semaglutide s.c. 1 mg		−1.05 [−1.19; −0.91]; <.0001	−4.35 [−4.94; −3.75]; <.0001
	Placebo			

Abbreviations: BID, twice-daily; CI, confidence interval; ETD, estimated treatment difference; exenatide ER, exenatide extended-release; exenatide ER AI, exenatide ER auto-injectable; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; NR, not recorded; NS, non-significant; QW, once-weekly; s.c., subcutaneous.

[a]ETD compared with exenatide BID treatment arm.

reductions in HbA_{1c} for each respective QW GLP-1 RA when compared with placebo, with mean treatment differences ranging between −0.53% and −1.75%.[6-8,15,24-29] In most trials, a similar trend was seen for body weight, with mean reductions of −0.68 to −5.06 kg being observed for QW GLP-1 RA treatment arms versus placebo.[6-8,15,24-29] In addition to different durations, these trials were conducted with a variety of treatment backgrounds, preventing cross-study comparisons of data (Table 2). Furthermore, to allow comparisons between concomitant therapies with and without active treatment, people with T2D randomized to placebo arms continued to receive standard-of-care anti-diabetic therapies according to each trial protocol. Thus, there were no 'true' placebos.

TABLE 3 HbA_{1c} and body weight change from trials that compared QW GLP-1 RAs with metformin and other oral anti-diabetics

Trial name, time until primary endpoint	Treatment arms	Permitted concomitant treatments	ETD HbA_{1c}, % [95% CI]; *P*-value	ETD body weight, kg [95% CI]; *P*-value
QW GLP-1 RAs compared with metformin (ETD vs metformin)				
AWARD-3[30], 26 weeks	Dulaglutide 0.75 mg	None	−0.15 [95% CI: NR]; .020	(−1.36 ± 0.24[a])
	Dulaglutide 1.5 mg		−0.22 [−0.36; −0.08]; .002	(−2.29 ± 0.24[a])
	Metformin			(−2.22 ± 0.24[a])
DURATION-4[31], 26 weeks	Exenatide ER 2 mg	None	(−1.53 ± 0.07[a])	(−2.0 ± 0.2[a])
	Metformin		(−1.48 ± 0.07[a]); .62	(−2.0 ± 0.2[a]); .892
QW GLP-1 RAs compared with DPP4is (ETD vs DPP4i)				
AWARD-5[69], 52 weeks	Dulaglutide 0.75 mg	Metformin	−0.47 [−0.63; −0.31]	−1.07 [95% CI: NR]; <.001
	Dulaglutide 1.5 mg		−0.71 [−0.87; −0.55]	−1.50 [95% CI: NR]; <.001
	Sitagliptin 100 mg (QD)			
	Placebo			
DURATION-2[70], 26 weeks	Exenatide ER 2 mg	Metformin	−0.6 [−0.9; −0.4]; <.0001	−1.5 [−2.4; −0.7]; .0002
	Sitagliptin 100 mg (QD)			
DURATION-4[31], 26 weeks	Exenatide ER 2 mg	None	(−1.53 ± 0.07[a])	(−2.0 ± 0.2[a])
	Sitagliptin 100 mg (QD)		(−1.15 ± 0.08[a]); <.001	(−0.8 ± 0.3[a]); <.001
DURATION-NEO-2[26], 28 weeks	Exenatide ER AI 2 mg	Metformin	−0.38 [−0.70; −0.06]; .021	0.1 [−0.7; 0.9]; NS
	Sitagliptin 100 mg (QD)			
SUSTAIN 2[71], 56 weeks	Semaglutide s.c. 0.5 mg	Metformin, pioglitazone, rosiglitazone	−0.77 [−0.92; −0.62]; <.0001	−2.35 [−3.06; −1.63]; <.0001
	Semaglutide s.c. 1 mg		−1.06 [−1.21; −0.91]; <.0001	−4.20 [−4.91; −3.49]; <.0001
	Sitagliptin s.c. 100 mg (QD)			
QW GLP-1 RAs compared with SGLT2is (ETD vs comparator arm, which included SGLT2i treatment)				
DURATION-8[59], 28 weeks	Exenatide ER 2 mg + Dapagliflozin 10 mg (QD)	Metformin		
	Exenatide ER 2 mg		−0.4 [−0.6; −0.1]; .004[b]	−1.87 [−2.66; −1.08]; <.001[b]
	Dapagliflozin 10 mg (QD)		−0.6 [−0.8; −0.3]; <.001[b]	−1.22 [−2.00; −0.44]; .002[b]
SUSTAIN 8[60]	Semaglutide s.c. 1 mg Canagliflozin 300 mg (QD)	Metformin	−0.5 [−0.65; −0.33]; <.0001	−1.06 [−1.76; −0.36]; .0029
SUSTAIN 9[55], 30 weeks	Semaglutide s.c. 1 mg	SGLT2is ± background ADT besides GLP-1 RAs DPP4is and AAs	−1.42 [−1.61, −1.24]; <.0001	−3.81 [−4.70, −2.93]; <.0001
	Placebo			
AWARD-10[54], 24 weeks	Dulaglutide 0.75 mg	SGLT2i ± Metformin	−0.66 [−0.84, −0.49]; <.0001	−0.5 [−1.3, 0.4]; .26
	Dulaglutide 1.5 mg		−0.79 [−0.97, −0.61]; <.0001	−0.9 [−1.8, −0.1]; .028
	Placebo			

Abbreviations: AA, amylin analogue; ADT, anti-diabetic treatment; BID, twice-daily; CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; ETD, estimated treatment difference; exenatide ER, exenatide extended-release; exenatide ER AI, exenatide ER auto-injectable; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; NS, non-significant; OAD, oral anti-diabetic; QD, once-daily; QW, once-weekly; SGLT2i, sodium-glucose cotransporter-2 inhibitor; s.c., subcutaneous; SU, sulphonylurea; TZD, thiazolidinedione.

[a]Least squares mean change from baseline ± standard error, *P*-value (if stated) is for between-group interaction.

[b]Combined treatment versus monotherapy.

TABLE 4 HbA_{1c} and body weight change from head-to-head GLP-1 RA trials

Trial name, time until primary endpoint	Treatment arms	Background treatments	ETD HbA_{1c}, % [95% CI]; *P*-value	ETD body weight, kg [95% CI]; *P*-value
QW vs QW				
SUSTAIN 3[39], 56 weeks	Semaglutide s.c. 1 mg	Metformin ± TZDs/SUs	−0.62 [−0.80; −0.44]; <.0001	−3.78 [−4.58; −2.98]; <.0001
	Exenatide ER 2 mg			
SUSTAIN 7[40], 40 weeks	Semaglutide s.c. 0.5 mg	Metformin	−0.40 [−0.55; −0.25]; <.0001	−2.26 [−3.02; −1.51]; <.0001
	Dulaglutide 0.75 mg			
	Semaglutide s.c. 1 mg		−0.41 [−0.57; −0.25]; <.0001	−3.55 [−4.32; −2.78]; <.0001
	Dulaglutide 1.5 mg			
QW vs QD/BID				
AWARD-1[15], 26 weeks	Dulaglutide 0.75 mg	Pioglitazone ± metformin	(−1.30 ± 0.06[a])	(0.20 ± 0.29[a])
	Dulaglutide 1.5 mg		(−1.51 ± 0.06[a])	(−1.30 ± 0.29[a])
	Exenatide 10μg BID		(−0.99 ± 0.06[a])	(−1.07 ± 0.29[a])
	Placebo		(−0.46 ± 0.08[a])	(1.24 ± 0.37[a])
AWARD-6[36], 26 weeks	Dulaglutide 1.5 mg	Metformin	−0.06 [0.19; 0.07]; <.0001[b]	−0.71 [0.17; 1.26]; .011
	Liraglutide 1.8 mg (QD)			
DURATION-5[37], 24 weeks	Exenatide ER 2 mg	Metformin, SUs, TZDs	−0.7 [−0.9; −0.4]; <.01	−0.95 [−1.9; 0.01]; NR[†]
	Exenatide 10 μg BID			
DURATION-6[38], 26 weeks	Exenatide ER 2 mg	Metformin, SU, metformin + SU, or metformin + pioglitazone	−0.21 [0.08; 0.33]; .0018	0.90 [0.39; 1.40]; .0005
	Liraglutide 1.8 mg (QD)			
SUSTAIN 10[35], 30 weeks	Semaglutide s.c. 1 mg	1–3 OADs	−0.69 [−0.82; −0.56]; <.0001	−3.83 [−4.57; −3.09]; <.0001
	Liraglutide 1.2 mg (QD)			

BID, twice-daily; CI, confidence interval; ETD, estimated treatment difference; exenatide ER, exenatide extended-release; exenatide ER AI, exenatide ER auto-injectable; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; NR, not reported; QD, once-daily; QW, once-weekly; s.c., subcutaneous; SU, sulphonylurea; TZD, thiazolidinedione.

[a]Least squares mean difference from baseline ± standard error.

[b]Significance for non-inferiority; [†]statistical significance not reported at Week 24.

3.2.1 | Relevance for pharmacists and other HCPs

The efficacy of GLP-1 RAs in regulating HbA_{1c} is well established and demonstrated across all clinical trials.[6-8,15,24-29] Semaglutide has consistently demonstrated substantial weight loss compared with placebo.[6,8,29] However, this is not true for all GLP-1 RAs,[24] and some doses demonstrated greater variability in this outcome than others in the class.[6,8,15,29] For example, in AWARD-1, people treated with dulaglutide 1.5 mg experienced both HbA_{1c} and body weight reductions, whereas those treated with dulaglutide 0.75 mg experienced HbA_{1c} reductions but without sustained body weight reductions.[15]

3.3 | QW GLP-1 RAs versus metformin

Metformin is recommended as first-line monotherapy for people with T2D unless contraindicated by severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), hypersensitivity to metformin, or acute chronic metabolic acidosis, although GLP-1 RAs are now recommended as a first-line monotherapy for people with T2D with atherosclerotic CV disease or high CV risk.[10,14] In addition, dual- or triple-combination therapies including metformin are recommended to help maintain glycaemic control in response to disease progression.[10] Due to metformin's widespread

use as a first-line treatment,[10] most clinical trials have allowed background treatment with metformin (Table 1).

Only two trials that directly compared QW GLP-1 RAs versus metformin have been included in this review (Table 3).[30,31] In AWARD-3, dulaglutide 1.5 mg was found to be superior to metformin in reducing HbA_{1c} (treatment difference −0.22%, 95% confidence interval [CI]: −0.36; −0.08; $P = .002$) but both groups had similar weight loss of ~2.2 kg from baseline (Table 3).[30] Exenatide ER in DURATION-4, however, proved only to be non-inferior to metformin for HbA_{1c} (–1.53% vs –1.48%, respectively) and, again, with similar levels of body weight reduction (both –2.0 kg).[31]

3.3.1 | Relevance for pharmacists and other HCPs

The efficacy and cost efficiency of metformin have meant that its use as a first-line therapy is well established and has been relied upon for a number of years.[32-34] However, the efficacy and CV benefits of GLP-1 RAs and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in people with T2D with high or very high CV risk have resulted in an adapted approach to T2D treatment, and GLP-1 RAs and SGLT2is are now recommended by the ESC as the first-line therapy in these patients.[14] It should be noted that there are currently no CVOTs conducted with metformin as a discrete treatment arm; therefore, the data supporting the CV benefits of metformin are weaker than for treatments such as GLP-1 RAs and SGLT2is.

3.4 | GLP-1 RA head-to-head trials

There are currently three QD or BID GLP-1 RAs available: exenatide BID,[18] liraglutide[19] and lixisenatide.[22] Seven within-class GLP-1 RA head-to-head trials are included in this review and summarized in Table 4, of which five compared QW with QD/BID[15,35-38] and two compared QW with QW.[39,40] Of the trials comparing a QW GLP-1 RA with exenatide BID, dulaglutide 1.5 mg was found to be superior to exenatide BID for HbA_{1c} reduction (treatment difference: −0.52%, 95% CI: −0.66%; −0.39%; $P < .001$) and yielded a similar degree of weight loss at 26 weeks.[15] Exenatide ER demonstrated superior reductions in HbA_{1c} (treatment difference: −0.7%, 95% CI: −0.9; −0.4; $P < .01$ at 24 weeks) versus exenatide BID, and with a large treatment difference in body weight reduction at the end of the trial.[37]

Three trials compared a QW GLP-1 RA with liraglutide QD.[35,36,38] Non-inferiority for HbA_{1c} reduction was shown for dulaglutide 1.5 mg versus liraglutide ≤1.8 mg in AWARD-6 at 26 weeks[36]; however, treatment with liraglutide ≤1.8 mg resulted in greater reductions in body weight by 0.71 kg (95% CI: 0.17; 1.26; $P = .011$).[36] In DURATION-6, exenatide ER was demonstrated to be inferior to liraglutide for both HbA_{1c} (treatment difference: 0.21%, 95% CI: 0.08; 0.33; $P = .0018$) and body weight reduction (treatment difference: 0.90 kg, 95% CI: 0.39; 1.40; $P = .0005$) at 26 weeks.[38] In SUSTAIN 10, semaglutide 1 mg demonstrated superiority when compared with liraglutide 1.2 mg for reduction in both HbA_{1c} (treatment difference: −0.69%, 95% CI: −0.82, −0.56; $P < .0001$) and body weight (treatment difference: −3.83 kg, 95% CI: −4.57; −3.09; $P < .0001$).[35]

The two trials that compared a QW GLP-1 RA with another QW GLP-1 RA were SUSTAIN 3 and 7, which investigated semaglutide 0.5 and 1 mg versus exenatide ER 2 mg[39] and dulaglutide 0.75 and 1.5 mg,[40] respectively. Each dose of semaglutide was found to provide superior glycaemic control and greater reductions in body weight than either comparator drug (Table 4). There are, at present, no data from head-to-head clinical trials comparing dulaglutide with exenatide ER.

As data from head-to-head trials are more robust than cross-trial comparisons, additional glycaemic control data derived from these sources were also investigated. In relation to fasting plasma glucose (FPG), QW GLP-1 RAs have been shown to yield similar reductions to QD GLP-1 RAs,[15,36,37,41] though not for all comparisons,[38] which is aligned with trends observed for mean HbA_{1c}. Within the QW class, treatment with semaglutide 1 mg resulted in greater FPG reductions than either dulaglutide 1.5 mg or exenatide ER 2 mg.[39,40]

QW GLP-1 RAs have also been shown to attenuate post-prandial glucose (PPG) excursions, with the greatest reductions observed for treatment with semaglutide 1 mg over either dulaglutide 1.5 mg or exenatide ER 2 mg.[39,40] Previously, it has been noted by Htike et al. that greater PPG reductions have been associated with shorter- versus longer-acting GLP-1 RA formulations,[42] though this is primarily true for the meal immediately following administration of the last dose.[43] PPG excursions have not been consistently reported across all trials[36-40] but may have clinically important implications.[15,35,44,45] Treatment with GLP-1 RAs have resulted in similar reductions of FPG levels,[39,40] although basal insulin glargine elicits superior FPG reductions compared with the GLP-1 RAs exenatide BID, exenatide QW, albiglutide and dulaglutide.[46-50]

3.4.1 | Relevance for pharmacists and other HCPs

These head-to-head trials demonstrate clear efficacy differences between QW GLP-1 RAs in terms of glycaemic control and body weight reduction (Table 4). However, costs of GLP-1 RAs are typically much higher than other add-on T2D therapies, and the burden of which is felt by healthcare systems and individuals whose insurance companies are reluctant to supplement the expenses.[51] Notwithstanding, it should be noted that the expense of GLP-1 RAs may be offset by the economic implications of glycaemic control and secondary effect on body weight seen with GLP-1 RAs, and patients may be willing to pay more for QW therapies that offer these benefits than QD treatments with a lower efficacy.[52] Nevertheless, the economic impact of GLP-1 RAs factor into prescribing decisions for people with T2D.[53] Although semaglutide is the most effective of the approved QW GLP-1 RAs for reducing HbA_{1c} and body weight,[39,40] exenatide ER and dulaglutide have also been shown to provide benefit compared with placebo.[6-8,15,24-27,29,54,55] It is, nonetheless, also important to

hold these efficacy differences within the broader context of each QW GLP-1 RA's overall benefit profile as the CV and renal benefits are not necessarily equivalent for all members of this class.

3.5 | QW GLP-1 RAs versus SGLT2is

SGLT2is prevent the reabsorption of glucose from the filtrate in the kidney and thus reduce overall blood sugar levels.[56,57] Consequently, this depletion of glucose and its associated calories in people with T2D with increased blood glucose mean that SGLT2is are the only other class of glucose-lowering drug along with GLP-1 RAs that routinely result in weight loss.[58]

Of the four trials involving QW GLP-1 RAs and SGLT2is, there are only two that investigated a QW GLP-1 RA and an SGLT2i as separate treatment arms: DURATION-8 (exenatide ER versus dapagliflozin)[59] and SUSTAIN 8 (semaglutide versus canagliflozin)[60] (Table 3). In SUSTAIN 8, it was found that treatment with semaglutide led to superior reductions in HbA_{1c} of −1.5% compared with −1.0% with canagliflozin, respectively.[60] A similar outcome was seen in DURATION-8, although the trial compared treatments as a monotherapy against the combination of both.[59] In this trial, it was found that combined treatment with exenatide ER and dapagliflozin yielded HbA_{1c} reductions of −2.0%, compared with −1.6% and −1.4% for exenatide ER and dapagliflozin monotherapies, respectively.[59] It should be noted that the baseline HbA_{1c} values for the population in this trial were higher than is typical (mean HbA_{1c} ~9%), with 57% of people with HbA_{1c} levels ≥9%.[59] This may have contributed to the larger HbA_{1c} reductions seen here than reported elsewhere, for example AWARD-8.[24]

The other two trials in this category, AWARD-10[54] and SUSTAIN 9,[55] assessed the efficacy of dulaglutide and semaglutide, respectively, as add-ons to SGLT2is. Both trials reported greater reductions for patients administered a QW GLP-1 RA versus placebo, with treatment differences in HbA_{1c} of −0.79% (95% CI: −0.97; −0.61; $P < .0001$) for dulaglutide 1.5 mg[54] and −1.42% (95% CI: −1.61; −1.24; $P < .0001$) for semaglutide 1 mg.[55] Concordantly, greater reductions in body weight versus placebo were also observed, with dulaglutide 1.5 mg yielding a treatment difference of −0.9 kg (95% CI: −1.8; −0.1; $P = .028$)[54] and semaglutide 1 mg −3.81 kg (95% CI: −4.70; −2.93; $P < .0001$).[55]

3.5.1 | Relevance for pharmacists and other HCPs

SGLT2is, which are all administered orally, provide a similar but complementary set of benefits to QW GLP-1 RAs, with greater HbA_{1c} and body weight reductions demonstrated in patients treated with a combination of both drug classes compared with those treated with either class individually.[54,55,59] Moreover, the pleiotropic benefits for each drug class, while similar, are non-identical and thus combination therapy may provide a broader set of overall benefits.[61,62] Both GLP-1 RAs and SGLT2is have shown promising results in CVOTs; SGLT2is have shown risk reductions of 14% for MACE in people with high-risk or established atherosclerotic CV disease in a meta-analysis[62,63] and reduced the risk of hospitalization for heart failure,[64,65] whereas GLP-1 RAs have been shown to reduce the frequency of MACE compared with placebo.[6,7,28] It remains to be seen whether the risk reduction in MACE observed for both drug classes is complementary in respect of combined therapy.

3.6 | QW GLP-1 RAs versus DPP4is

Endogenous GLP-1 is degraded by the enzyme dipeptidyl peptidase-4 (DPP4).[66] An alternative approach to raising incretin responses in people with T2D has been treatment with drugs that inhibit the proteolytic activity of DPP4 (DPP4 inhibitors [DPP4is]).[67] It should be noted that the HbA_{1c} reductions seen with DPP4is result from the action of persevered endogenous GLP-1, which is diminished in people with T2D.[68] Five clinical trials that directly compared a QW GLP-1 RA with a DPP4i have been included in this review (Table 3).

In four of these trials, GLP-1 RAs were superior to DPP4is in terms of HbA_{1c} reduction, with treatment differences for the highest drug doses ranging from −0.38% to −1.06%;[26,69-71] patients treated with semaglutide versus sitagliptin demonstrated the greatest differences.[71] This trend also extended to body weight, with most trials demonstrating superior reductions in patients administered QW GLP-1 RAs versus DPP4is.[69-71] Treatment differences ranged from −1.07 kg to −4.20 kg, and the greatest differences were observed in patients treated with semaglutide.[71]

3.6.1 | Relevance for pharmacists and other HCPs

Generally, DPP4is are considered to be weight-neutral[67] and to result in fewer adverse events, such as nausea, than GLP-1 RAs.[26,31,69,71,72] Overall, this may suggest that DPP4is are suitable for use in specific circumstances where weight loss is unimportant or should be treated with caution (eg older populations[73,74]) and the diminished reductions in HbA_{1c} are acceptable or where GLP-1 RAs are contraindicated.[10] However, DPP4is do not confer the same CV and renal benefits as demonstrated for some GLP-1 RAs[5-7,75-77]; thus, such factors must be considered when making treatment decisions.[10]

3.7 | QW GLP-1 RAs versus insulin

The progressive nature of T2D typically results in a need for basal insulin injections in order to maintain adequate glycaemic control, and insulin is recommended when HbA_{1c} reaches levels >10%.[10] There are five clinical trials included in this review that directly compare the efficacy of QW GLP-1 RAs with insulin-based treatments (Table 5).[9,50,78-80] It should be noted that, as insulin has no maximal dose and is typically titrated upwards until clinical targets are met,

efficacy results such as glycaemic control need to be considered within the broader clinical benefit and safety profile (eg hypoglycaemia or weight) of the comparator. Additionally, as the method of insulin titration varies from trial to trial, the validity of cross-trial comparisons is especially limited.

In all trials included within this review, QW GLP-1 RAs were demonstrated to be at least as effective as insulin-based treatments in regaining glycaemic control (Table 5).[9,50,78-80] When factoring in other endpoints such as hypoglycaemic events and weight gain, the greatest treatment benefits compared with insulin were observed with semaglutide, followed by dulaglutide and then exenatide ER.[78-80] Moreover, in one trial, dulaglutide was compared with insulin glargine in people with chronic kidney disease, a common complication of T2D.[9] Dulaglutide at both 0.75 and 1.5 mg demonstrated non-inferiority to insulin glargine in terms of HbA_{1c} reduction but with an increased eGFR.[9]

Three trials examined the effect of QW GLP-1 RAs administered in combination with insulin.[25,27,29] In these, all three QW GLP-1 RAs compared with placebo have been shown to further reduce HbA_{1c} when combined with insulin (Table 5),[25,27,29] with semaglutide

TABLE 5 HbA_{1c} and body weight change from trials that compared QW GLP-1 RAs with insulin

Trial name, time until primary endpoint	Treatment arms	Permitted concomitant treatments	ETD HbA_{1c}, % [95% CI]; *P*-value	ETD body weight, kg [95% CI]; *P*-value
QW GLP-1 RAs vs insulin (ETD vs insulin)				
AWARD-2[78], 52 weeks	Dulaglutide 0.75 mg	Metformin, glimepiride	−0.13 [−0.29; −0.02]; <.001	−1.33 ± 0.24[a]; <.001
	Dulaglutide 1.5 mg		−0.45 [−0.60; −0.29]; <.001	−1.87 ± 0.24[a]; <.001
	Insulin glargine			1.44 ± 0.24
AWARD-4[50], 26 weeks	Dulaglutide 0.75 mg	Metformin, insulin lispro	−0.17 [−0.33; −0.02]; .015	0.18 [−0.35; 0.71][a,b]; <.0001
	Dulaglutide 1.5 mg		−0.22 [−0.38; −0.07]; .005	−0.87 [−1.40; −0.34][a,b]; <.0001
	Insulin glargine			2.33 [1.80, 2.86][b]; <.0001
AWARD-7[9], 26 weeks	Dulaglutide 0.75 mg	Insulin lispro	0.02 [−0.18; 0.22]; .0001[c]	NR
	Dulaglutide 1.5 mg		−0.05 [−0.26; 0.15]; .0001[c]	NR
	Insulin glargine			
DURATION-3[79], 156 weeks	Exenatide ER 2 mg	Metformin ± SUs	−0.20 [−0.39; −0.02]; .03	−4.51 [−5.23; −3.79]; <.001
	Insulin glargine			
SUSTAIN 4[80], 30 weeks	Semaglutide s.c. 0.5 mg	Metformin ± SUs	−0.38 [−0.52; −0.24]; <.0001	−4.62 [−5.27; −3.96]; <.0001
	Semaglutide s.c. 1 mg		−0.81 [−0.96; −0.67]; <.0001	−6.33 [−7.00; −5.68]; <.0001
	Insulin glargine			
QW GLP-1 RAs in combination with insulin (ETD vs placebo)				
AWARD-9[25], 28 weeks	Dulaglutide 1.5 mg	Insulin glargine ± metformin	−0.77 [0.97; −0.56] <.001	−2.41 [−3.19; −1.64]; <.001
	Placebo			
DURATION-7[27], 28 weeks	Exenatide ER 2 mg	Insulin glargine ± (metformin ± SU)	−0.73 [−0.93; −0.53]; <.001	−1.5 [−2.17; −0.84]; <.001
	Placebo			
SUSTAIN 5[29], 30 weeks	Semaglutide s.c. 0.5 mg	Basal insulin ± metformin	−1.35 [−1.61; −1.10]; <.0001[†]	−2.31 [−3.33; −1.29]; <.0001[†]
	Semaglutide s.c. 1 mg		−1.75 [−2.01; −1.50]; <.0001[†]	−5.06 [−6.08; −4.04]; <.0001[†]
	Placebo			

Abbreviations: BID, twice-daily; CI, confidence interval; ETD, estimated treatment difference; exenatide ER AI, exenatide ER auto-injectable; exenatide ER, exenatide extended-release; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; NR, not reported; QD, once-daily; QW, once-weekly; s.c., subcutaneous; SU, sulphonylurea.

[a]*P*-values represent dulaglutide versus insulin glargine.

[b]Adjusted mean change from baseline [95% CI].

[c]Significance for non-inferiority; [†]compared against placebo.

achieving the greatest treatment difference of −1.75% (95% CI: −2.01; −1.50; $P < .0001$) and a reduction in body weight of −5.06 kg (95% CI: −6.08; −4.04; $P < .0001$).[29]

3.7.1 | Relevance for pharmacists and other HCPs

Insulin remains the most potent antihyperglycaemic agent but carries the risk of hypoglycaemia and weight gain.[10,13] Recent changes to treatment guidelines from the ADA, American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), ACC/AHA and EASD recommend prescribing GLP-1 RAs prior to insulin-based medications in cases where first-line metformin is failing to reach appropriate glycaemic targets.[10-13] Although GLP-1 RAs are also an injectable antihyperglycaemic medication, QW formulations require substantially fewer injections overall than using a daily basal insulin and do not carry a high risk of hypoglycaemia.[10] However, the risk of hypoglycaemia is increased when GLP-1 RAs are used in conjunction with insulin, which should result in a reduced insulin dose.[17-22]

3.8 | CV results

In addition to these standard Phase 3 trial outcomes (HbA_{1c}, FPG, PPG and body weight), specifically designed Phase 3 trials have examined CV outcomes (detailed in the sister article[81]). To summarize the results pertaining to the three QW GLP-1 RAs, people with T2D and previous CV disease that were treated with exenatide ER versus placebo did not demonstrate any statistically significant risk reduction for MACE.[28] In contrast, in SUSTAIN 6, it was shown that people with T2D and at high risk of CV events who were treated with semaglutide experienced a significant reduction in first occurrence of MACE (post hoc analysis, hazard ratio [HR] 0.2645; 95% CI: 0.58; 0.95; $P = .02$) compared with placebo.[6] Similarly, in REWIND, dulaglutide also provided a significant risk reduction in first occurrence of MACE or death from unknown causes (HR 0.88; 95% CI: 0.79; 0.99; $P = .026$).[7]

3.9 | 3.9. Renal results

Renal outcomes are also important for people with T2D and have been reported inconsistently across clinical trials included in this review, with such data reported in only six of the primary publications.[6,7,9,27,28,79] Of these, AWARD-7 explicitly assessed renal outcomes in people with chronic kidney disease and established that dulaglutide achieved similar levels of glycaemic control to insulin glargine U100 but with a reduced decline in eGFR.[9] In the three QW GLP-1 RA CVOTs,[6,7,28] new or worsening nephropathy was seen in fewer patients treated with semaglutide[6] and dulaglutide[7] but not exenatide ER compared with placebo.[28] In DURATION-3[79] and DURATION-7,[27] however, no significant differences were reported for renal measurements (urinary albumin-to-creatinine ratio or eGFR) in patients treated with exenatide ER compared with insulin glargine or placebo (on a background of insulin glargine), although renal outcomes were not the primary endpoints of these analyses.

4 | DISCUSSION

Due to variations between trials that were included within this review in terms of design, duration, background medications and clinical endpoints, only the head-to-head trials could provide robust comparisons between each of the QW GLP-1 RAs. Therefore, the relative efficacy for glycaemic control and weight reduction for drugs within the QW class of GLP-1 RAs is only truly evaluable for semaglutide versus either exenatide ER or dulaglutide.[39,40] In SUSTAIN 3, semaglutide 1 mg was superior to exenatide ER 2 mg for reductions in HbA_{1c} and body weight.[39] In SUSTAIN 7, patients treated with semaglutide 0.5 mg and 1 mg versus dulaglutide 0.75 and 1.5 mg experienced greater reductions of HbA_{1c} and body weight.[40] Additionally, the frequency of GI disorders was similar for the highest doses of dulaglutide (48%) and both doses of semaglutide (44%), whereas the lowest frequency of GI disorders was seen with dulaglutide 0.75 mg (33%).[40] The increased weight reduction in patients treated with semaglutide is notable when compared with either dulaglutide[40] or exenatide ER.[39]

These benefits of QW GLP-1 RAs must be weighed against reported adverse events, of which GI problems predominate. These are, however, typically early-onset and transient in nature;[8,50,80] nonetheless, in cases where GI problems are of particular concern, the use of alternative treatments to GLP-1 RAs, GLP-1 RAs associated with lower rates of GI problems, or lower doses may be worthwhile considerations. The nature of GI problems and actions to mitigate their impact should also be communicated to people with T2D treated with GLP-1 RAs.

In recent studies, other possible pleiotropic effects of QW GLP-1 RAs have been considered, with one of the main parameters evaluated being CV outcomes[6,7,9,28]; while exenatide ER did not demonstrate any statistically significant risk reduction for MACE versus placebo,[28] semaglutide (post hoc test)[6] and dulaglutide[7] did.

Similarly, the potential renal benefits of QW GLP-1 RAs have been measured in some trials,[6,7,9,27,28,79] but the evidence is stronger for dulaglutide[7,9] and semaglutide[6] compared with exenatide ER.[27,28,79] Such differences in these pleiotropic effects may form part of treatment decisions and discussions with patients.

ADA and EASD guidelines have changed in response to the proven pleiotropic benefits of GLP-1 RAs in the body and now recommend the use of GLP-1 RAs as the first injectable antihyperglycaemic agent ahead of insulin.[10,12] Importantly, there are also clear benefits of the concomitant use of GLP-1 RAs alongside other antihyperglycaemic agents such as SGLT2is. Both GLP-1 RAs and SGLT2is have shown promising results in CVOTs for people with CV disease or at high risk of CV disease[6,7,61,62] and have additive

advantages for both HbA_{1c} and weight reduction when used in combination.[54,55,59] Additionally, as they offer different CV benefits,[62] the combination of both is likely to be preferable to either treatment alone, though the actual results from the combination treatments are not available.

In terms of combination therapy, however, current data provide an incomplete picture, as there are no head-to-head CVOTs in T2D available that compare multiple, different combinations of drugs from different classes as distinct, controlled, treatment arms. This is unlikely to change, given the ethical implications of randomizing patients to receive placebo throughout the long duration of CVOTs when there are a number of potential combination therapies available. Nonetheless, there is the possibility that certain combinations may interact in unforeseen ways and prove more or less efficacious than others.

Similarly, the clinical trials within this review do not provide the necessary data to effectively evaluate how patients may adhere to QW GLP-1 RA treatment in the real world, and there are presently few available studies that assess this. However, based on data from retrospective, observational studies, adherence benefits are apparent for QW compared with QD formulations of GLP-1 RAs.[82,83] Nonetheless, data are still limited, and although QW GLP-1 RAs have demonstrated glycaemic and body weight efficacy within the context of clinical trials (Tables 2–5), it is now increasingly important to assess the post-approval, real-world, long-term effectiveness of each QW GLP-1 RA with respect to both glycaemic and pleiotropic clinical goals. These assessments will then need to be considered alongside the emerging clinical profiles of pharmacological agents that are currently under development, such as an oral version of semaglutide that will require QD administration.[84,85]

5 | WHAT IS NEW AND CONCLUSION

Recent changes to several guidelines (including ADA, EASD and ESC) prioritize the use of GLP-1 RAs due to the associated CV benefits before advancing to treatment with basal insulin or even metformin[10-13] and, thus, all HCPs need to be aware of the differences within this class. As data from clinical trials are being published regularly, with data from nine trials published between 2018 and 2019,[7,9,27,29,35,39,40,54,55] this review collated the efficacy data to help inform those involved in treatment decisions of and discussions with people with T2D. Based on current data, in terms of glycaemic control, QW semaglutide appears to be the most efficacious QW GLP-1 RA, particularly when used in combination with agents from other drug classes such as SGLT2is or insulin. There are also clinical benefits from treatment with QW GLP-1 RAs that extend beyond glycaemic control, such as weight loss and CV protection. However, these do not seem to apply to all QW GLP-1 RAs to the same extent; therefore, due consideration of the differences between agents within this drug class is required when making prescription choices.

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CONFLICTS OF INTEREST

D Patel is an advisory board member and/or consultant for AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk and Sanofi; and is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Merck, Novo Nordisk and Valeritas.

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