ADA 2026 highlights: Therapies in development for type 2 diabetes, obesity, dyslipidaemia and liver disease

The 2026 Scientific Sessions of the American Diabetes Association were held in New Orleans on 5–8 June. Data on novel oral and injectable therapies, for management of glycaemia, weight, dyslipidaemia and steatotic liver disease, were presented. With a growing list of diabetes and obesity treatment options that are likely to reach us in the future, in this meeting report we attempt to keep abreast of the evidence and outline the key highlights from the Sessions.

Phase 3 studies: Diabetes and obesity drugs

Orforglipron – oral GLP-1 receptor agonist shows benefits over other glucose-lowering therapies in type 2 diabetes

Data from three phase 3 studies of orforglipron, a small-molecule oral GLP-1 receptor agonist that can be taken orally with no dosing restrictions on food or drink consumption, were presented at the Sessions with accompanying publications. All studies were from the ACHIEVE programme, evaluating the safety and efficacy of orforglipron for management of glycaemia in people with type 2 diabetes. Although approved in the US for weight management, orforglipron is not approved in the UK for any indication at the time of writing.

ACHIEVE-2: Orforglipron versus dapagliflozin

ACHIEVE-2 was a 40-week, open-label trial of orforglipron versus dapagliflozin conducted in 962 adults with type 2 diabetes with an HbA_{1c} of 53–91 mmol/mol (7.0–10.5%) despite treatment with metformin. All were randomised to orforglipron 3 mg, 12 mg or 36 mg, or to dapagliflozin 10 mg, daily.

Across all tested doses, orforglipron met criteria for both non-inferiority and superiority versus dapagliflozin. Mean HbA_{1c} reductions were 13.4, 16.4 and 17.0 mmol/mol with orforglipron 3 mg, 12 mg and 36 mg, respectively, compared with 8.9 mmol/mol with dapagliflozin (P<0.001 for all comparisons with dapagliflozin).

Higher orforglipron doses provided additional metabolic benefits. The 12 mg and 36 mg doses produced greater weight loss than dapagliflozin, with dose-dependent reductions in body weight and a higher likelihood of achieving meaningful weight loss thresholds. The 36 mg dose also improved several cardiometabolic risk markers versus dapagliflozin, including triglycerides, non-HDL cholesterol and systolic blood pressure.

Orforglipron's adverse event profile was typical of the GLP-1 RA class: mostly gastrointestinal and generally mild to moderate in severity, occurring mainly during dose escalation and attenuating over time. However, discontinuations due to adverse events were more common with orforglipron than with dapagliflozin.

The study was simultaneously published in *The Lancet*.

ACHIEVE-3: Orforglipron versus oral semaglutide at doses approved for type 2 diabetes

ACHIEVE-3 was a 52-week, open-label study comparing orforglipron 12 mg or 36 mg versus oral semaglutide 7 mg or 14 mg in 1698 adults with type 2 diabetes and suboptimal glycaemic control despite metformin therapy.

At 52 weeks' follow-up, for the treatment regimen estimand (i.e. based on data from all those enrolled in the study irrespective of discontinuation or additional treatments needed), mean HbA_{1c} had fallen (from 67 mmol/mol [8·3%] at baseline) by 18.7 and 20.9 mmol/mol with orforglipron 12 mg and 36 mg, respectively, versus 13.4 and 16.0 mmol/mol with oral semaglutide 7 mg and 14 mg. Both non-inferiority and superiority in terms of HbA_{1c} reduction were demonstrated with both doses of orforglipron versus semaglutide.

Adverse events were typical of the class; however, gastrointestinal events, discontinuations due to adverse events and a mean increase in pulse rate were more common with orforglipron.

The study was previously published in *The Lancet*. A more detailed summary can be found in *Diabetes Distilled*.

ACHIEVE-5: Orforglipron versus placebo as an add-on to basal insulin

ACHIEVE-5 was a 40-week, double-blind study evaluating the safety and efficacy of orforglipron 3 mg, 12 mg or 36 mg in adults with type 2 diabetes taking insulin glargine, with or without metformin and/or SGLT2 inhibitors.

Among the 546 participants randomised to orforglipron or placebo (median diabetes duration 14.6 years), 507 completed the trial. HbA_{1c} at 40 weeks was reduced by 17.2–20.5 mmol/mol in orforglipron recipients, versus 8.6 mmol/mol with placebo (P<0.001 for all comparisons). Mean body weight fell by 2.6–5.4% with orforglipron, and by 0.2% with placebo. The risk of clinically significant hypoglycaemia was not higher with orforglipron versus placebo.

Lead author Francesco Giorgino (University of Bari Aldo Moro, Italy) commented on the results, saying: "For many patients, basal insulin alone is not enough to maintain glycaemic control, and an oral GLP-1 therapy could offer a simpler alternative to intensifying insulin treatment while giving healthcare professionals greater flexibility in managing care."

The study was simultaneously published in *JAMA*.

Retatrutide – triple receptor agonist for weight loss and glucose control

Data on retatrutide, a triple agonist of GLP-1, GIP and glucagon currently in development, were presented, showing benefits for weight loss and glycaemic control, as well as obstructive sleep apnoea and knee pain.

Weight management (no diabetes)

In the phase 3 TRIUMPH-1 trial, once-weekly subcutaneous retatrutide at doses of 4 mg, 9 mg and 12 mg was compared with placebo in 2339 participants with obesity, including a subset with knee osteoarthritis and/or obstructive sleep apnoea. After 80 weeks of treatment, weight was reduced by 19.0%, 25.9% and 28.3% from baseline with retatrutide 4 mg, 9 mg and 12 mg, respectively. Placebo recipients, in contrast, saw a reduction of 2.2%.

Significant improvements from baseline in triglycerides, systolic blood pressure and high-sensitivity C-reactive protein were also observed in retatrutide recipients, along with reductions in knee pain and sleep disturbances.

Type 2 diabetes management

In the phase 3 TRANSCEND-T2D-1 randomised controlled trial, monotherapy with injectable once-weekly retatrutide was compared with placebo in 537 people with type 2 diabetes and suboptimal glycaemic control. After 40 weeks of treatment, for the treatment regimen estimand, HbA_{1c} was reduced by 18.5, 20.3 and 21.2 mmol/mol in the retatrutide 4 mg, 9 mg and 12 mg groups, respectively, compared with a reduction of 8.9 mmol/mol with placebo (P<0.001 for all comparisons).

Mean reductions in baseline body weight ranged from 11·5% to 15·3% with retatrutide, versus 2·6% with placebo. Improvements in LDL cholesterol, triglycerides and blood pressure were also observed and the adverse event profile was similar to GLP-1-based therapies currently in use.

The study was published simultaneously in *The Lancet*.

Survodutide – dual GLP-1/glucagon receptor agonist shows benefits in obesity and MASLD

Results of two phase 3 trials of survodutide, a once-weekly dual agonist of GLP-1 and glucagon in development, were presented, showing benefits in people with obesity and metabolic dysfunction-associated steatotic liver disease (MASLD).

Weight management (no diabetes)

In the SYNCHRONIZE-1 trial, 725 people with obesity and at least one obesity complication (excluding type 2 diabetes) were assigned 1:1:1 to receive subcutaneous survodutide 3.6 mg or 6.0 mg, or placebo, in conjunction with lifestyle advice. At 76 weeks' treatment, for the treatment regimen estimand, mean body weight had fallen by 12.2% and 13.0% with survodutide 3.6 mg and 6.0 mg, respectively, compared with 5.4% in the placebo group (P<0.001 for both comparisons with placebo).

Interestingly, in a prespecified subgroup of participants who underwent MRI, among those receiving the higher dose of survodutide (n=25), body fat analysis showed reductions of 27.8% in total body fat, 34.0% in visceral fat, 63.1% in liver fat and 9.8% in lean mass. In placebo recipients (n=25), these reductions were 9.5%, 11.8%, 24.5% and 2.9%, respectively. The authors speculated that this may indicate beneficial effects of survodutide on body composition beyond mere weight loss, likely as a result of glucagon receptor agonism.

However, side-effects, particularly gastrointestinal, were common and led to discontinuation in many (up to 20% of participants receiving the higher dose of survodutide).

This trial was simultaneously published in the *New England Journal of Medicine*.

Management of MASLD

The SYNCHRONIZE-MASLD trial enrolled 216 adults with obesity and at least one weight-related condition (including type 2 diabetes in 40%), in addition to MASLD or metabolic dysfunction-associated steatohepatitis (MASH). Participants were randomised 2:1 to survodutide 6.0 mg or placebo for 48 weeks. The primary endpoints were weight loss and liver fat content, as measured with MRI.

At 48 weeks, according to the treatment efficacy estimand, 68.5% of survodutide recipients had a ≥30% reduction in liver fat, versus 28.6% of placebo recipients. Body weight fell by 8.7% versus 1.4%. The mean relative reduction in liver fat (efficacy estimand) was 58.7% with survodutide versus 9.5% with placebo.

As with SYNCHRONIZE-1, adverse events were common, mostly gastrointestinal and occurring during dose escalation, and led to discontinuation in 20% of survodutide recipients versus 4% of

placebo recipients. The study was limited by its short duration and was conducted in the US and Spain only.

Commenting on the two studies for the PCDO Society, co-author Carel le Roux (University College Dublin) said that retatrutide "leads to substantial weight loss but, more importantly, it drives fat down in the compartments that are associated with better cardiovascular outcomes."

CagriSema (fixed-dose combination of GLP-1 RA plus amylin analogue)

Results of the REIMAGINE clinical trials of CagriSema, a fixed-dose combination of cagrilintide and semaglutide, were presented at the Sessions. Cagrilintide is a long-acting analogue of amylin, a pancreatic hormone that signals satiety after eating.

REIMAGINE 1: Monotherapy for type 2 diabetes management

In the phase 3a REIMAGINE 1 study, two doses of once-weekly CagriSema (2.4 mg or 1.0 mg doses of both drugs) were compared with placebo in 189 adults with type 2 diabetes. Participants were early in their diabetes journey and had a mean HbA_{1c} of 62 mmol/mol (7.8%) despite management with diet and lifestyle.

After 40 weeks of treatment, according to the treatment efficacy estimand, HbA_{1c} had fallen by 19.7 and 16.4 mmol/mol in the two CagriSema groups, respectively, versus a fall of 1.1 mmol/mol with placebo. Weight fell by 13.8% with high-dose CagriSema and by 11.8% with the lower dose, compared with a 1.4% reduction in placebo recipients.

The safety profile was consistent with previous studies of GLP-1 RAs and cagrilintide, with mild-to-moderate gastrointestinal adverse events being the most common. Adverse events occurred in 75–79% of CagriSema recipients versus 66% of placebo recipients.

The authors concluded that cagrilintide–semaglutide is a potential novel and effective therapeutic intervention for people with early-stage type 2 diabetes.

The study was simultaneously published in *The Lancet Diabetes & Endocrinology*.

REIMAGINE 2: CagriSema versus cagrilintide or semaglutide alone in type 2 diabetes

REIMAGINE 2 was a 68-week study comparing CagriSema versus its individual components or placebo in 2728 people with type 2 diabetes and an HbA_{1c} of 53–91 mmol/mol (7.0–10.5%) despite treatment with metformin ± an SGLT2 inhibitor.

Results showed that CagriSema (2.4 mg of both agents) lowered HbA_{1c} more than semaglutide 2.4 mg alone (estimated treatment difference 1.7 mmol/mol [0.16%]; P=0.0035), with slightly more adverse events than with the individual therapies.

The study was simultaneously published in *The Lancet Diabetes & Endocrinology*.

REIMAGINE 3: CagriSema in people with type 2 diabetes taking basal insulin

In contrast to the previous two studies conducted in people with earlier-stage type 2 diabetes, REIMAGINE 3 was conducted in 274 people with long-standing diabetes being treated with basal insulin therapy (with or without metformin).

Over a period of 40 weeks, significantly greater reductions in HbA_{1c} were observed with the higher and lower doses of CagriSema (25.5 and 23.0 mmol/mol, respectively) compared with placebo (7.2 mmol/mol) (P<0.001 for both comparisons). Body weight reductions of 10–12% also occurred in CagriSema recipients. No cases of severe hypoglycaemia were reported.

The authors concluded that their findings support the use of CagriSema as an add-on to once-daily basal insulin to significantly improve glycaemic control.

The study was simultaneously published in *The Lancet*.

Lipid-lowering therapies

Evolocumab: Primary cardiovascular protection with PCSK9 inhibitor in people with high-risk diabetes

The VESALIUS-CV trial evaluated the efficacy of the PCSK9 inhibitor evolocumab for preventing first cardiovascular events in people at high cardiovascular risk. Results of a prespecified subgroup analysis of 6002 participants with high-risk diabetes (microvascular disease, insulin use or diabetes duration ≥10 years) were presented at the Sessions.

All of the 6002 participants had an LDL cholesterol level of ≥90 mg/dL (≥2.3 mmol/L, approximately), and 67% were on a high-intensity statin and 24% on an SGLT2 inhibitor or GLP-1 receptor agonist at baseline. All were randomised to evolocumab 140 mg or placebo every 2 weeks. Median LDL had fallen significantly in evolocumab recipients after 48 weeks (to 1.2 mmol/L, versus 2.8 mmol/L with placebo).

At a median follow-up of 4.6 years, evolocumab reduced the risk of 3-point major adverse cardiovascular events (MACE; death due to coronary heart disease, non-fatal myocardial infarction or non-fatal ischaemic stroke) by 29% and the risk of 4-point MACE (previous three outcomes plus ischaemia-driven arterial revascularisation) by 21% compared with placebo. Myocardial infarction risk was reduced by 35% and all-cause mortality by 21%.

Results were consistent regardless of the presence or absence of qualifying atherosclerosis, baseline LDL level, statin intensity, or use of SGLT2 inhibitors or GLP-1 RAs.

These results were simultaneously published in *Diabetes Care*.

Olezarsen reduces triglycerides and risk of acute pancreatitis in people with severe hypertriglyceridaemia

Olezarsen is a developmental therapy that inhibits apolipoprotein C-III, a protein that slows the breakdown of triglycerides and thus increases their levels in the blood. Data from the CORE-TIMI 72a and 72b phase 3 trials of olezarsen were presented, specifically comparing outcomes between people with and without diabetes.

In the two trials, a combined 1063 adults with severe hypertriglyceridaemia (≥500 mg/dL; equivalent to ≥5.6 mmol/L) were randomised to olezarsen (50 mg or 80 mg) or placebo for 12 months. The primary outcome was percentage change in triglyceride levels and secondary outcomes included risk of acute pancreatitis.

Overall, 63% of participants had diabetes at baseline. At the 6-month follow-up, compared with placebo, olezarsen 50 mg and 80 mg reduced triglyceride levels by 57.4% and 64.8% in this subgroup. Risk of acute pancreatitis was also reduced, by 81% in the two olezarsen groups combined, compared with placebo (absolute risk reduction 6.6%, equivalent to a number needed to treat of 16 to prevent one event over 1 year).

Minor increases in HbA_{1c} (around 3 mmol/mol) were observed in olezarsen recipients. Thrombocytopenia and elevations in liver enzymes were more common with the 80 mg dose of olezarsen, and a dose-dependent increase in hepatic fat fraction was observed.

An open-label study extension is ongoing and should provide insight into the long-term efficacy and safety of olezarsen in this high-risk population.

Phase 2 studies: Quick highlights

Acmopatide – first incretin therapy developed specifically for type 1 diabetes

A phase 2 study of acmopatide, a dual GIP/GLP-1 receptor agonist in development specifically to expand treatment options for type 1 diabetes, were presented.

In 111 adults with type 1 diabetes and a BMI ≥27 kg/m^2, acmopatide reduced HbA_{1c} by 3.7 mmol/mol (0.34%) compared with placebo at 16 weeks, and 56% of participants achieved an HbA_{1c} below 53 mmol/mol (7.0%).

Acmopatide also led to dose-dependent weight loss of up to around 7% and reduced insulin use by up to 15%, compared with placebo. The treatment was generally well tolerated, with no reported safety concerns.

Elecoglipron – oral, once-daily, small-molecule GLP-1 receptor agonist for type 2 diabetes and weight management

The phase 2b SOLSTICE trial, simultaneously published in *The Lancet*, evaluated the efficacy, safety and tolerability of elecoglipron in adults with type 2 diabetes and inadequate glycaemic management.

Over 26 weeks in 404 participants, clinically meaningful reductions in HbA_{1c} and body weight were observed, with the highest dose of elecoglipron (75 mg) achieving a mean reduction in HbA_{1c} of 20.8 mmol/mol, compared with 2.2 mmol/mol in the placebo group. The highest dose also resulted in significant body weight reductions of 7.7%, compared with 1.7% in placebo recipients.

Meanwhile, the phase 2b VISTA trial, also published in *The Lancet*, evaluated elecoglipron for weight management in 310 adults with obesity, or with overweight and at least one weight-related condition (excluding type 2 diabetes).

At 26 weeks, average body weight reductions with elecoglipron ranged from 2.6% (5 mg dose) to 10.5% (75 mg dose), compared with a 0.6% reduction in placebo recipients. Improvements in cardiometabolic measures, including blood pressure and C-reactive protein levels, were also observed with elecoglipron.

Berobenatide – ultra-long-acting GLP-1 receptor agonist for weight and type 2 diabetes management

Berobenatide is an ultra-long-acting GLP-1 receptor agonist which is being investigated for potential monthly dosing. Data from the VESPER-1 and VESPER-2 trials suggested that once-weekly injections of the agent provided effective weight loss in people with obesity, with and without type 2 diabetes. VESPER-3 was a phase 2b trial evaluating whether berobenatide could successfully transition from once-weekly to once-monthly dosing while still maintaining weight loss and tolerability.

Results suggested that monthly dosing remained effective, demonstrating weight loss and favourable tolerability. After 28 weeks of treatment, berobenatide demonstrated placebo-adjusted weight loss of up to 12.3% with the 4.8 mg monthly dose. Safety and tolerability were consistent with the GLP-1 RA class.

The study is ongoing, with the final endpoint being evaluated at 64 weeks. ■

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