Zenagamtide (amycretin), a novel unimolecular GLP-1 and amylin receptor agonist: phase 2 results in T2D

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Presenter disclosures

- Pablo Mora has received honoraria for serving on advisory committees from Abbott, Biomea Fusion, Dexcom, Insulet, Medtronic and Novo Nordisk; and has served on speaker bureau for Abbott, Dexcom, Eli Lilly, Insulet, Medtronic and Novo Nordisk

Background and aim

Amylin and GLP-1 receptor agonists have distinct mechanisms of action but complementary physiological effects on glycemic control, body weight and other cardiometabolic parameters[1–3]

Zenagamtide (formerly known as amycretin) is a unimolecular peptide agonist of GLP-1 and amylin receptors

In adults with overweight or obesity, once-weekly subcutaneous zenagamtide has demonstrated significantly greater reductions in body weight (up to 24.3%) than placebo (up to 1.1%), with a safety/tolerability profile consistent with those of GLP-1 and amylin receptor agonists[4]

This phase 2 trial is the first clinical evaluation of zenagamtide in T2D

Aim

This trial assessed the efficacy and safety of once-weekly subcutaneous and once-daily oral zenagamtide vs placebo in adults with T2D. Here, we report the once-weekly subcutaneous zenagamtide data

GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes

1. Eržen S *et al. Int J Mol Sci* 2024;25:1517; **2.** Drucker DJ *et al. Lancet* 2006;368:1696–705; **3.** Frias JP *et al. Lancet* 2023;402:720–30; **4.** Dahl K *et al. Lancet* 2025;406:149–62

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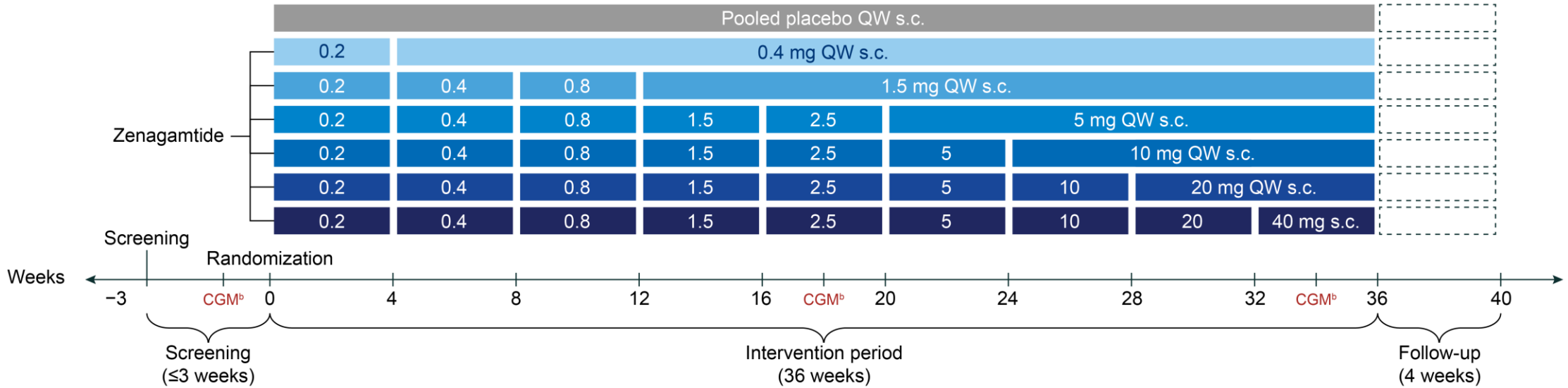
Once-weekly subcutaneous zenagamtide: trial design[a]

A 36-week, randomized, double-blind (within-treatment group), placebo-controlled, dose-finding, phase 2 trial



Adults (aged 18–75 years) with T2D (A1C 7.0–10.0%) and a BMI ≥23.0 and <50.0 kg/m^2 treated with stable doses of metformin with or without an SGLT2i were randomized (6:1) to once-weekly subcutaneous zenagamtide or placebo before being randomized (1:1:1:1:1:1) to zenagamtide 0.4, 1.5, 5, 10, 20 or 40 mg or matched placebo

ClinicalTrials.gov: NCT06542874
[a]Trial design for once-daily oral zenagamtide reported separately
[b]Blinded CGM periods starting at week −2, week 18 and week 34, lasting approximately 10 days each. Participants were provided with a Dexcom G6 CGM device (Dexcom, San Diego, CA, USA)
A1C, glycated hemoglobin; BMI, body mass index; CGM, continuous glucose monitoring; QW, once weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor; s.c., subcutaneously; T2D, type 2 diabetes

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Demographics and baseline characteristics

	Zenagamtide 0.4 mg (n=38)	Zenagamtide 1.5 mg (n=36)	Zenagamtide 5 mg (n=37)	Zenagamtide 10 mg (n=38)	Zenagamtide 20 mg (n=38)	Zenagamtide 40 mg (n=38)	Pooled placebo (n=37)
Male, n (%)	23 (61)	23 (64)	23 (62)	26 (68)	26 (68)	26 (68)	26 (70)
Age, years	56.0±10.4	56.9±8.8	57.0±10.2	57.6±9.1	58.0±9.3	57.2±9.0	57.2±10.6
A1C, %	8.0±0.8	7.7±0.9	7.8±0.7	7.9±0.8	7.7±0.6	7.8±0.8	8.0±0.7
Diabetes duration, years	8±8	8±5	10±11	9±7	6±6	8±7	8±6
Body weight, kg	102.4±25.2	99.9±20.2	98.9±20.1	95.8±21.0	98.4±21.0	99.5±25.2	99.8±22.8
BMI, kg/m²	35.3±6.6	34.8±6.7	33.7±6.2	32.9±6.4	32.7±5.4	32.9±6.1	33.9±5.9
SGLT2i use at randomization, n (%)	16 (42)	10 (28)	16 (43)	14 (37)	16 (42)	16 (42)	16 (43)

- In total, 262 participants were randomized; 191 completed trial treatment
- Most treatment discontinuations were attributed to adverse events (16.8% of total participants), mainly related to nausea and vomiting, with the largest number of discontinuations reported in the higher dose treatment groups

All values are arithmetic mean±standard deviation unless otherwise specified
A1C, glycated hemoglobin; BMI, body mass index; SGLT2i, sodium-glucose co-transporter-2 inhibitor

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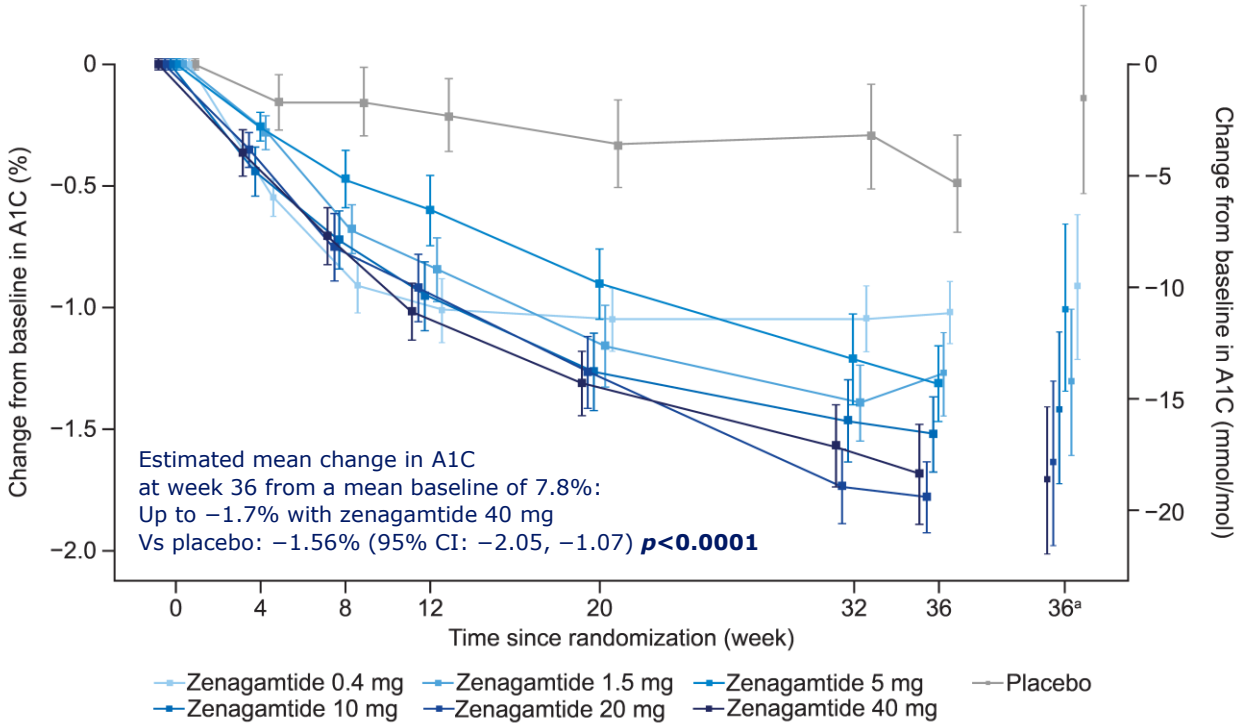
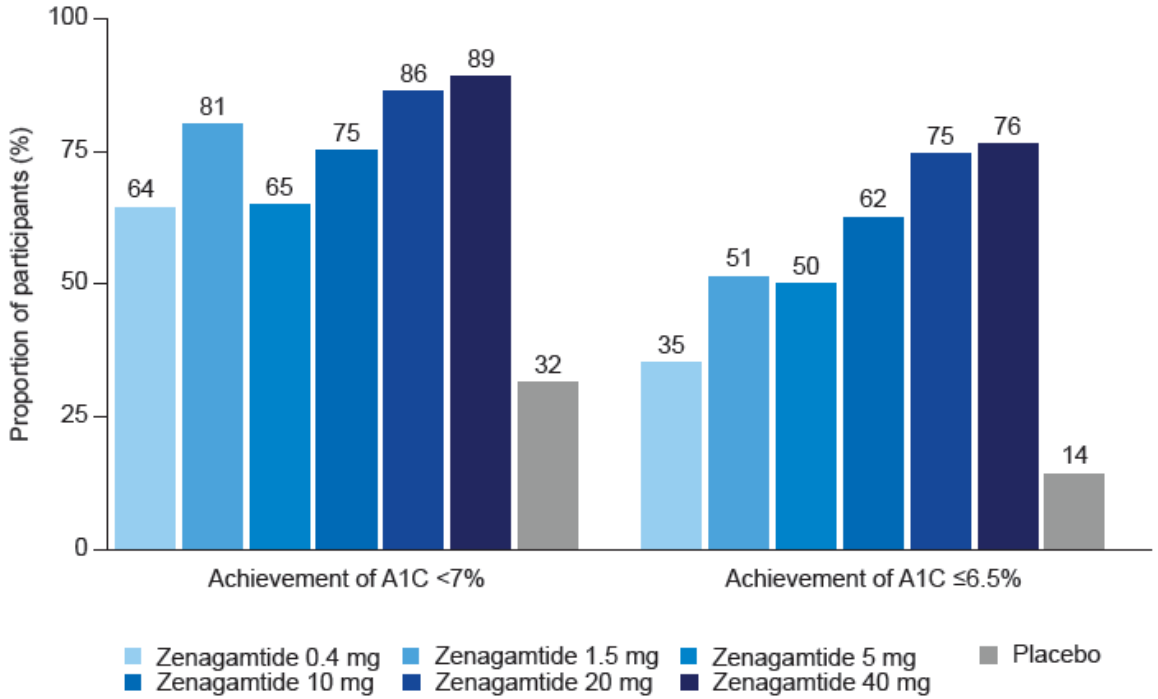
Key outcomes

Mean change in A1C from baseline to week 36



Proportion of participants achieving A1C targets at week 36



Error bars show standard error of the mean

[a]Estimated values from statistical analysis. Each endpoint was analyzed using an ANCOVA model with the endpoint as dependent variable, randomized treatment and strata as fixed factors, and baseline assessment corresponding to the endpoint as a fixed covariate. Missing data were imputed using multiple imputation and data from the on-treatment without rescue medication observation period, as defined by the primary estimand

A1C, glycated hemoglobin; ANCOVA, analysis of covariance; CI, confidence interval

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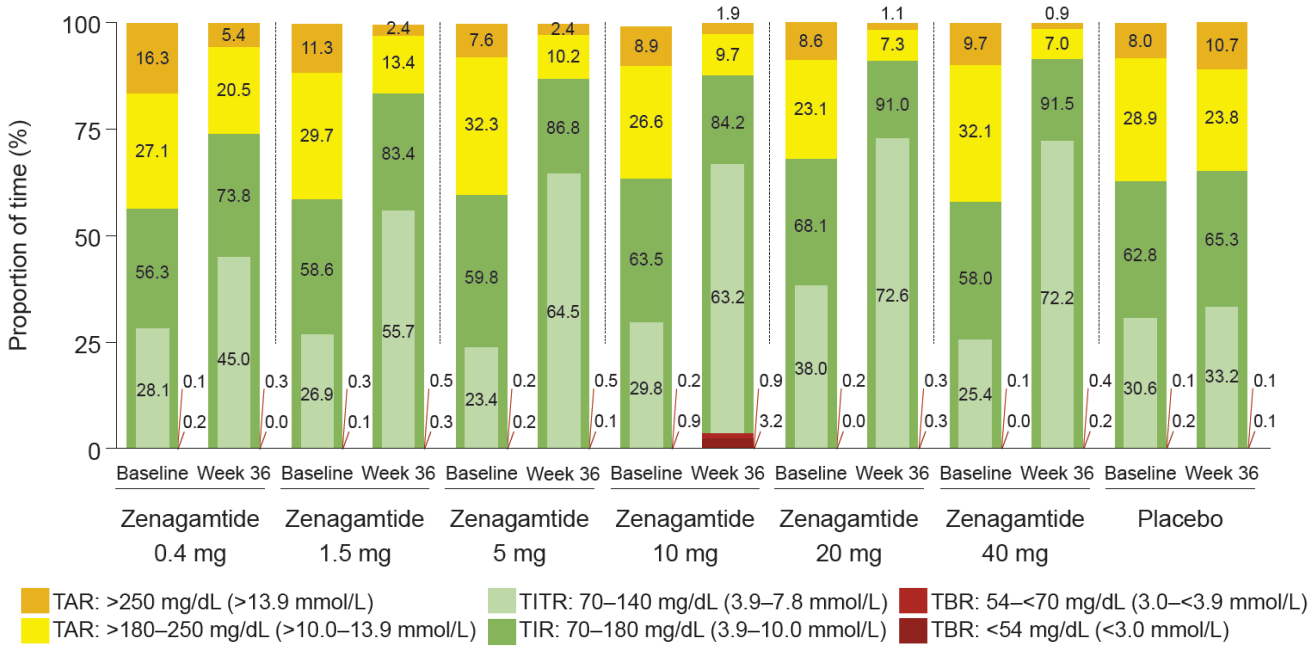
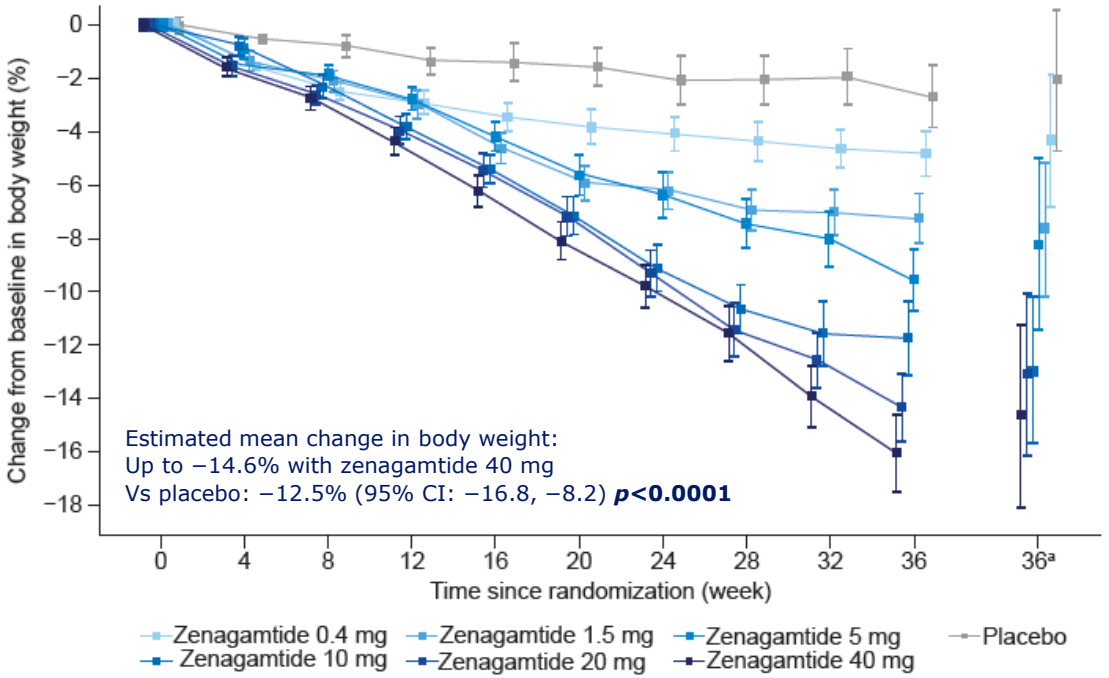
Key outcomes

CGM metrics at baseline and week 36



Mean change in body weight from baseline to week 36



Error bars show standard error of the mean. CGM assessments are averages calculated over a 10-day period. Proportions of time in ranges are observed values

[a]Estimated values from statistical analysis. Each endpoint was analyzed using an ANCOVA model with the endpoint as dependent variable, randomized treatment and strata as fixed factors, and baseline assessment corresponding to the endpoint as a fixed covariate. Missing data were imputed using multiple imputation and data from the on-treatment without rescue medication observation period as defined by the primary estimand

A1C, glycated hemoglobin; ANCOVA, analysis of covariance; CGM, continuous glucose monitoring; CI, confidence interval; TAR, time above range; TBR, time below range; TIR, time in range; TITR, time in tight range

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Zenagamtide had a dose-dependent effect on SBP, hsCRP and lipids

SBP: estimated change from baseline to week 36 was up to −10.63 mmHg with zenagamtide 40 mg (vs placebo: −7.13 [95% CI: −19.24, 4.98]; *p*=0.25)

HsCRP: Estimated ratio to baseline at week 36 was as low as 0.31 with zenagamtide 40 mg (ETR vs placebo: 0.26 [95% CI: 0.09, 0.76]; *p*=0.015)

Triglycerides and total cholesterol: Estimated ratios from baseline to week 36 were as low as 0.58 (ETR vs placebo: 0.52 [95% CI: 0.38, 0.71]; *p*<0.0001) and 0.85 (ETR vs placebo: 0.88 [95% CI: 0.76, 1.01]; *p*=0.074) with zenagamtide 40 mg, respectively

HDL cholesterol: Estimated ratio from baseline to week 36 was up to 1.13 with zenagamtide 40 mg (ETR vs placebo: 1.14 [95% CI: 1.04, 1.24]; *p*=0.0044)

CI, confidence interval; , estimated treatment difference; ETR, estimated treatment ratio; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure

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Adverse events

	Zenagamtide 0.4 mg (n=38)		Zenagamtide 1.5 mg (n=36)		Zenagamtide 5 mg (n=37)		Zenagamtide 10 mg (n=38)		Zenagamtide 20 mg (n=38)		Zenagamtide 40 mg (n=38)		Pooled placebo (n=36)	
	N (%)	E (R)	N (%)	E (R)	N (%)	E (R)	N (%)	E (R)	N (%)	E (R)	N (%)	E (R)	N (%)	E (R)
Adverse events														
Total adverse events	26 (68)	89 (3.0)	24 (67)	73 (2.8)	27 (73)	114 (4.0)	26 (68)	101 (3.5)	34 (90)	203 (7.0)	34 (90)	202 (6.8)	21 (58)	68 (2.6)
Serious adverse events	4 (11)	5 (0.2)	3 (8)	5 (0.2)	2 (5)	2 (0.1)	5 (13)	6 (0.2)	3 (8)	6 (0.2)	1 (3)	1 (<0.1)	3 (8)	5 (0.2)
Severe adverse events	2 (5)	3 (0.1)	2 (6)	3 (0.1)	0	–	5 (13)	7 (0.2)	3 (8)	6 (0.2)	4 (11)	6 (0.2)	0	–
Probably or possibly related to trial product	12 (32)	42 (1.5)	14 (39)	35 (1.3)	22 (59)	63 (2.5)	22 (58)	65 (2.5)	29 (76)	144 (5.95)	32 (84)	131 (5.2)	10 (28)	17 (0.7)
Action – trial treatment withdrawn	3 (8)	3 (0.1)	1 (3)	1 (<0.1)	6 (16)	6 (0.2)	8 (21)	12 (0.5)	13 (34)	22 (0.8)	13 (34)	24 (0.8)	2 (6)	3 (0.1)
Gastrointestinal adverse events														
Nausea	4 (11)	26 (0.9)	6 (17)	7 (0.3)	14 (38)	16 (0.6)	10 (26)	18 (0.6)	19 (50)	42 (1.4)	14 (37)	37 (1.3)	5 (14)	6 (0.2)
Vomiting	1 (3)	1 (<0.1)	1 (3)	3 (0.1)	6 (16)	11 (0.4)	4 (11)	6 (0.2)	9 (24)	19 (0.7)	11 (29)	16 (0.5)	2 (6)	2 (0.1)
Diarrhea	2 (5)	2 (0.1)	2 (6)	3 (0.1)	4 (11)	7 (0.2)	4 (11)	5 (0.2)	6 (16)	14 (0.5)	14 (37)	20 (0.7)	2 (6)	2 (0.1)
Adverse events of special interest														
Hypoglycemia[a]	0	–	0	–	0	–	0	–	1 (3)	1 (<0.1)	0	–	0	–
Dysesthesia[b]	0	–	0	–	0	–	3 (8)	3 (0.1)	2 (5)	2 (0.1)	8 (21)	10 (0.4)	0	–

[a]Severe hypoglycemia (level 3): hypoglycemia with severe cognitive impairment requiring external assistance for recovery. [b]Evaluated using prespecified customized cluster of MedDRA preferred terms
%, proportion of participants; AE, adverse event; E, number of events; MedDRA: Medical Dictionary for Regulatory Activities; N, number of participants; R, event rate per person-year of exposure

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Trial limitations

- The higher zenagamtide dose treatment groups were only exposed to the maintenance dose for a short period of time (20 mg for 8 weeks and 40 mg for 4 weeks)
- Participants were blinded to treatment group (zenagamtide vs placebo) but not to dose level

Conclusions

Once-weekly subcutaneous zenagamtide up to 40 mg demonstrated clinically meaningful and statistically significant improvements in glycemic control (A1C [up to −1.7%] and CGM-based metrics) and body weight (up to −14.6%), with no apparent plateau in weight loss, vs placebo

The safety and tolerability profile of subcutaneous zenagamtide was consistent with those of other GLP-1- and amylin-based therapies[1]

The benefits of zenagamtide as a potential therapeutic option for weight management and T2D will be assessed further in phase 3 trials

A1C, glycated hemoglobin; CGM, continuous glucose monitoring; GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes

1. Dahl K et al. *Lancet* 2025;406(10499):149-62

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