

Zenagamtide, a novel, long-acting, unimolecular GLP-1 and amylin receptor agonist, does not delay gastric emptying

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Introduction



GLP-1 receptor agonists have demonstrated clinically significant reductions in body weight, and additional benefits including reductions in CV risk, and improvements in symptoms associated with heart failure, CKD, and MASH¹⁻⁵



Amylin, a peptide hormone co-secreted with insulin, regulates body weight by reducing appetite and energy intake, and increasing satiety through the activation of the AMYR⁶



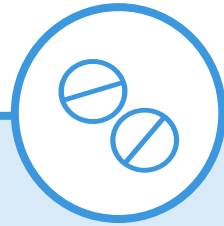
Zenagamtide (NNC0487-011) is a novel, long-acting, unimolecular GLP-1 receptor, AMYR and calcitonin agonist with oral and s.c. formulations under development for weight management and T2D treatment^{7,8}

1. Sanyal AJ et al. *N Engl J Med* 2025;392:2089–2099; 2. Perkovic V et al. *N Engl J Med* 2024;391:109–121; 3. Wilding JPH et al. *N Engl J Med* 2021;384:989–1002; 4. Lincoff AM et al. *N Engl J Med* 2023;389:2221–2232; 5. Deanfield J et al. *Lancet* 2024;404:773–786; 6. Lutz TA. *Appetite* 2022;172:105965; 7. Gasiorek A et al. *Lancet* 2025;406:135–148; 8. Dahl K et al. *Lancet* 2025;406:149–162. AMYR, amylin receptor; CKD, chronic kidney disease; CV, cardiovascular; GLP-1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; s.c., subcutaneous; T2D, type 2 diabetes.

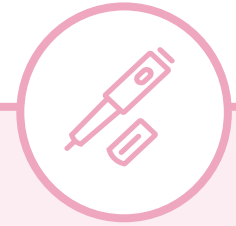
Introduction



A previous preclinical study showed zenagamtide activates GLP-1, amylin and calcitonin receptors in human, mouse and rat cell-based systems, and targets areas of the mouse brain that regulate food intake¹



In a previous phase 1 study in participants with overweight or obesity, OD oral zenagamtide (up to 2 × 50 mg) led to a mean reduction in body weight of up to **13.1%** at 12 weeks compared with 1.2% with placebo, with no weight loss plateau²



In a phase 1b/2a study, once-weekly s.c. zenagamtide (up to 60 mg) led to a mean reduction in body weight of up to 24.3% compared with 1.1% with placebo, with no signs of weight loss reaching a nadir after 36 weeks of treatment³



The aim of the current study was to evaluate the effect of oral and s.c. zenagamtide on gastric emptying

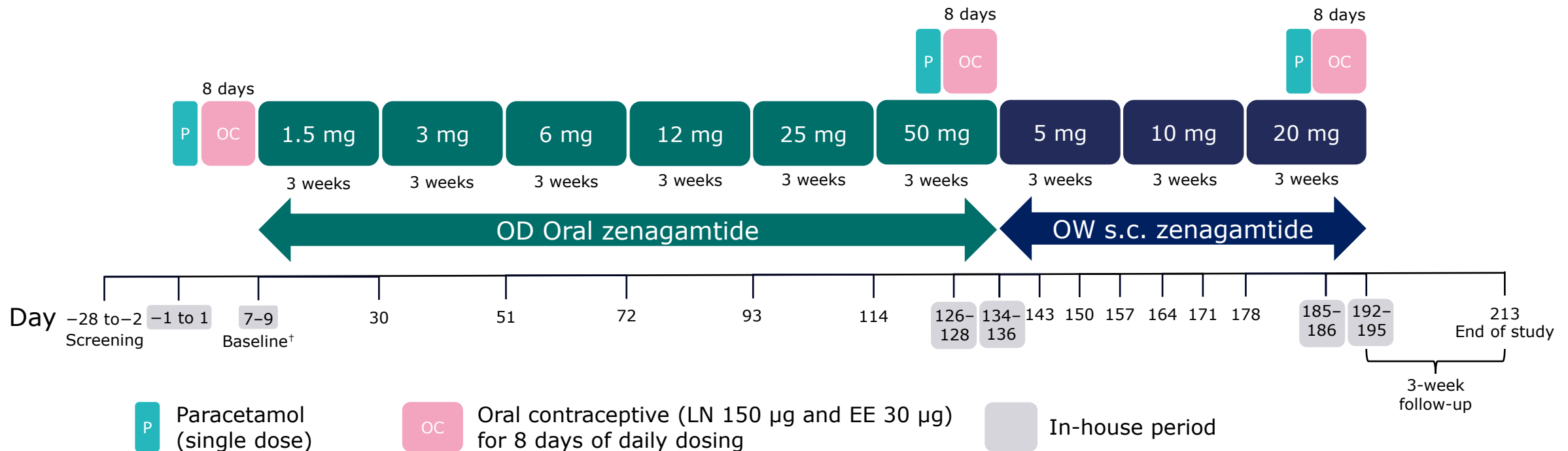
1. Kuhre RE et al. *EBioMedicine* 2025;118:105862; 2. Gasiorek A et al. *Lancet* 2025;406:135–148; 3. Dahl K et al. *Lancet* 2025;406:149–162.

GLP-1, glucagon-like peptide-1; OC, oral contraceptive; OD, once daily; PK, pharmacokinetics; s.c., subcutaneous.

Gabe MBN et al. Presented at the 33rd European Congress on Obesity (ECO), 12–15 May 2026, Istanbul, Türkiye.

Study design

A single-centre, one-sequence, crossover, open-label study (NCT06461039) that investigated the effects of zenagamtide on gastric emptying using the paracetamol absorption test and on the PK of a combined OC



Gastric emptying was investigated using the paracetamol absorption test as part of a standardised meal, with paracetamol PK sampled pre-dose and for 5 hours post-meal and post-dose

[†]Baseline measurement defined as the latest available measurement at or prior to the administration of zenagamtide.

EE, ethinylestradiol; LN, levonorgestrel; OC, oral contraceptive; OD, once daily; OW, once weekly; P, paracetamol; PK, pharmacokinetics; s.c., subcutaneous.

Gabe MBN et al. Presented at the 33rd European Congress on Obesity (ECO), 12–15 May 2026, Istanbul, Türkiye.

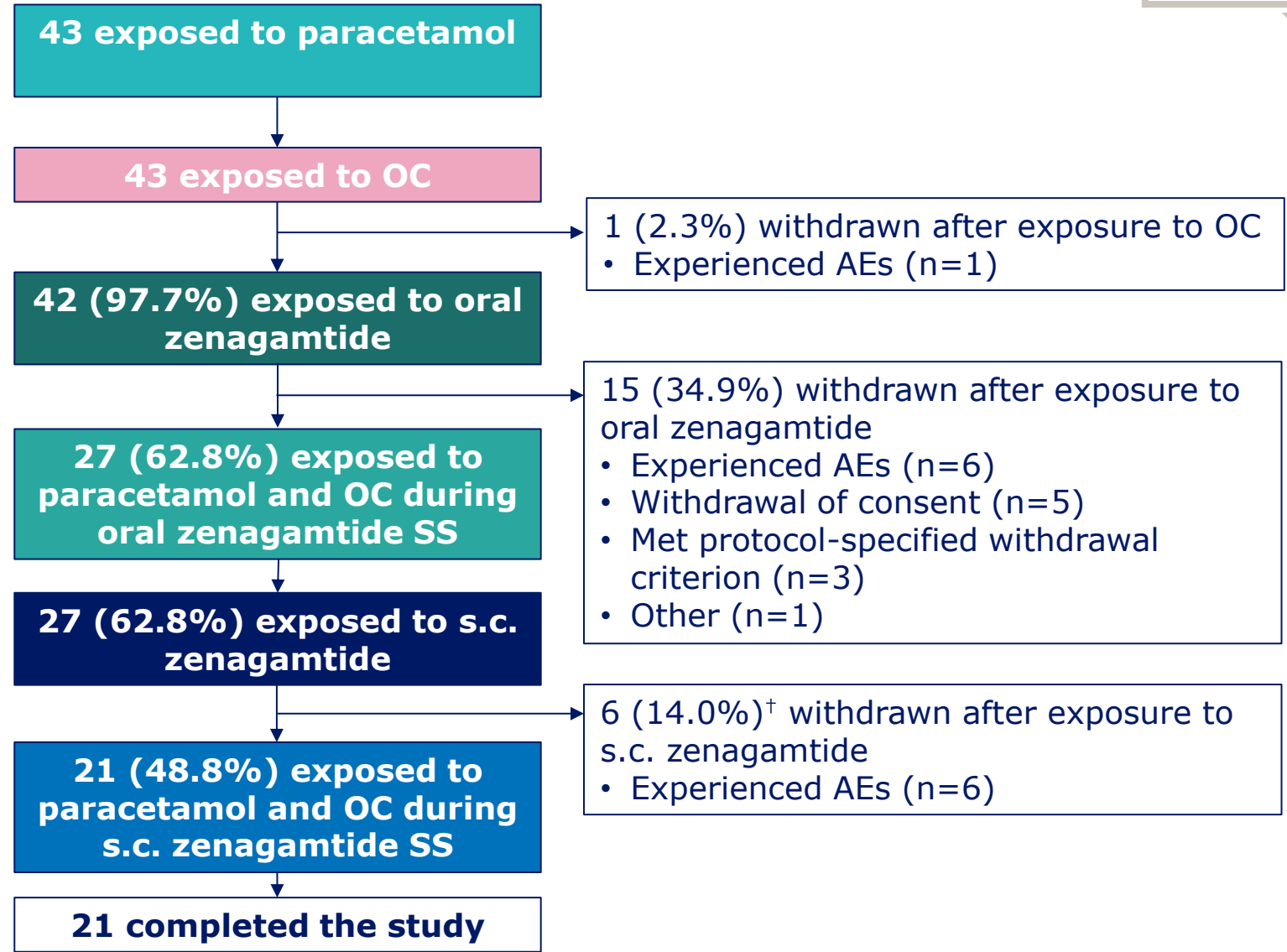
Study design (2/2)

Population 	Female participants of non-childbearing potential aged 18–65 years with a BMI between 25.0–39.9 kg/m ²
Procedures 	Gastric emptying was initially assessed at baseline. This was followed by once-daily oral zenagamtide, with dose escalation every third week to reach SS for the 50 mg dose, at which point gastric emptying was assessed again. Participants were then switched to once-weekly s.c. zenagamtide, with dose escalation every third week to reach SS for the 20 mg dose, at which point gastric emptying was assessed for the final time
Outcomes 	Endpoints at oral and s.c. zenagamtide SS were paracetamol AUC _{0–60min} and AUC _{0–300min} , C _{max} and t _{max}
Statistics 	Endpoints were log transformed and analysed using an analysis of variance model. Endpoints were also assessed with log of body weight as a time-dependent covariate

AUC, area under the curve; BMI, body mass index; C_{max}, maximum concentration; s.c., subcutaneous; SS, steady-state; t_{max}, time to C_{max}.

Participant flow

- In total, AEs leading to withdrawal occurred in seven participants in the oral zenagamtide dosing period, while four AEs occurred in the s.c. zenagamtide dosing period
- These AEs were mainly related to gastrointestinal disorders, were mild to moderate in severity and the majority had resolved by end of study



Two participants were withdrawn due to AEs occurring during the oral zenagamtide treatment period; however, they were only exposed to one dose of s.c. zenagamtide before withdrawal.

[†]One of these participants was withdrawn due to AEs experienced during both oral and s.c. zenagamtide dosing periods.

AE, adverse event; OC, oral contraceptive; s.c., subcutaneous; SS, steady state.

Participant baseline demographics

In total, 43 participants were included in the study

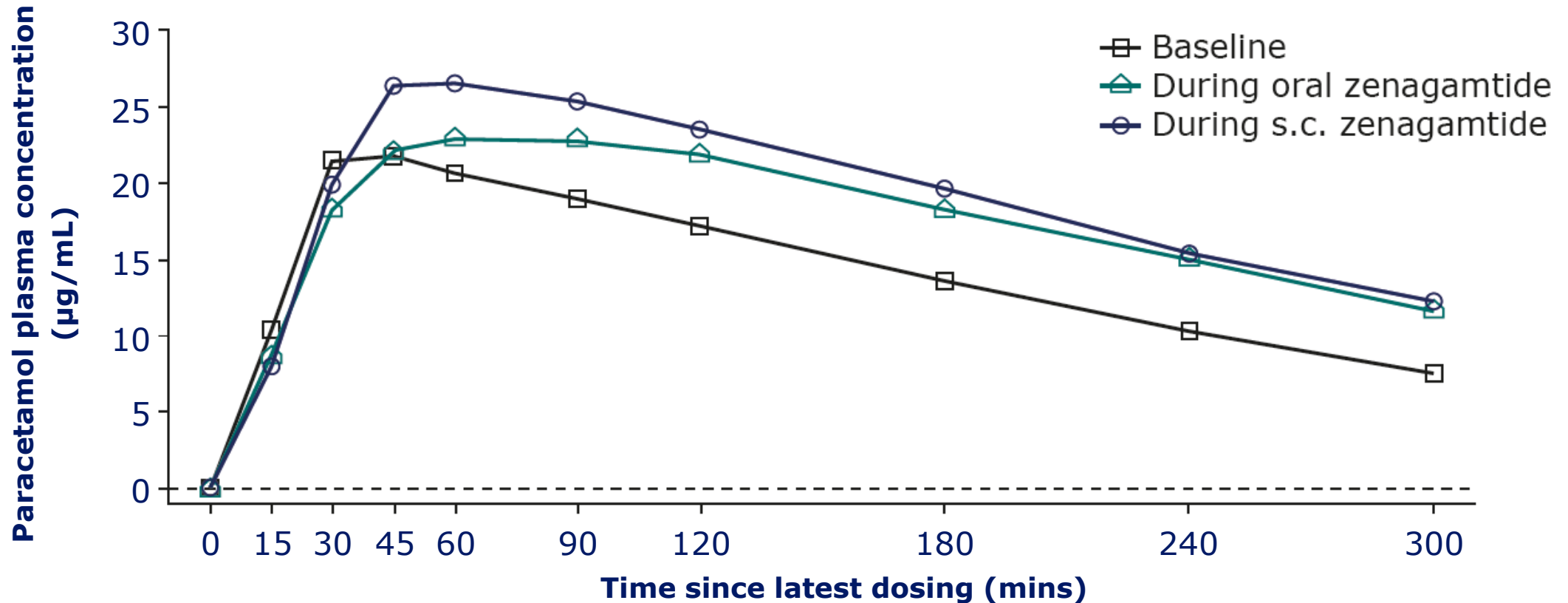
Mean (SD) age: 53.5 (7.1) years
Mean (SD) BMI: 30.0 (3.4) kg/m²

	Total (N=43)
Race, n (%)	
White	40 (93.0)
Multiple	2 (4.7)
Black or African American	1 (2.3)
Ethnicity, n (%)	
Hispanic or Latino	9 (20.9)
Not Hispanic or Latino	34 (79.1)
Age, years, mean (SD)	53.5 (7.1)
Min; max	31.0; 65.0
Body weight, kg, mean (SD)	79.5 (11.1)
Min; max	59.7; 103.4
BMI, kg/m ² , mean (SD)	30.0 (3.4)
Min; max	25.5; 38.9
HbA _{1c} , %, mean (SD)	5.3 (0.3)
Min; max	4.6; 6.0

Baseline measurement is defined as the latest available measurement at or prior to the administration of zenagamtide.

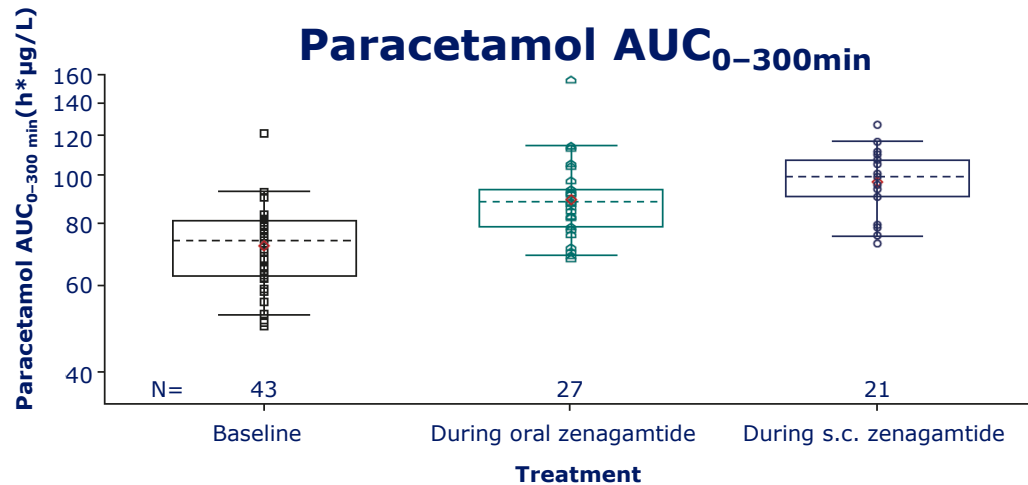
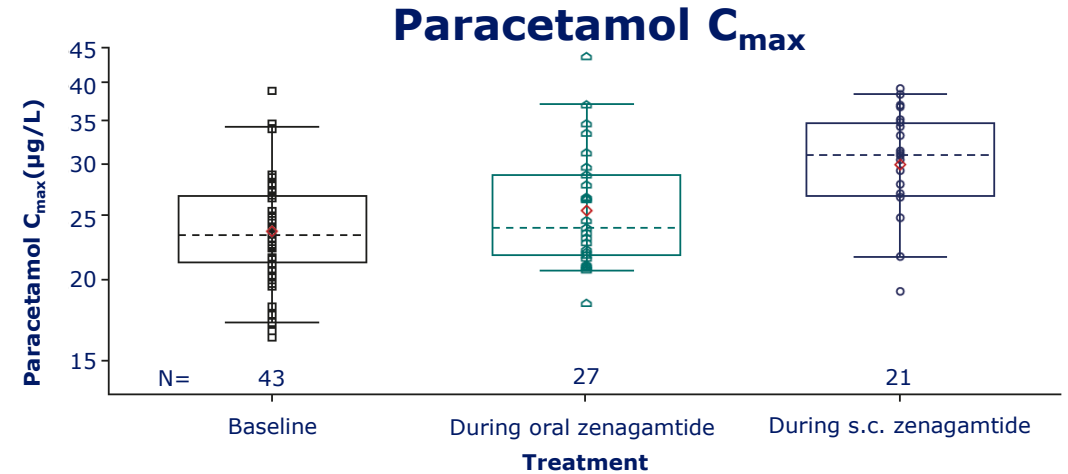
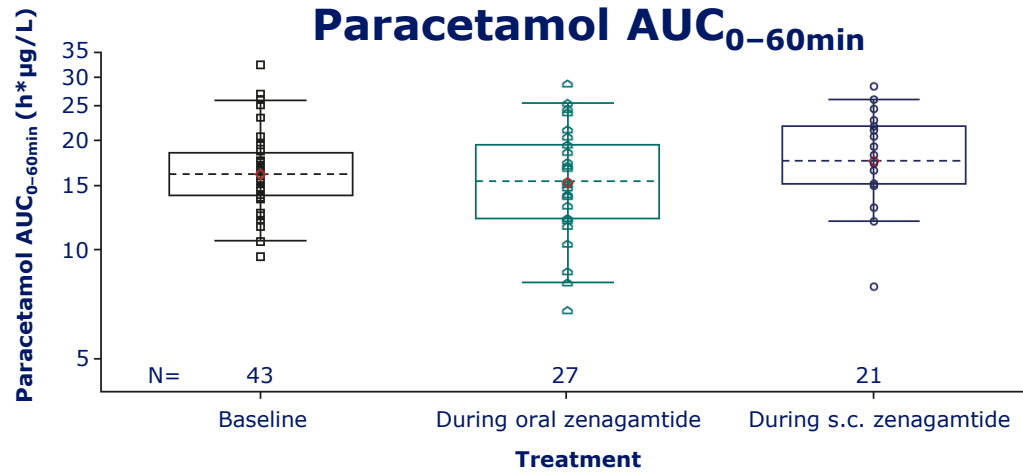
BMI, body mass index; HbA_{1c}, glycated haemoglobin; N, total number of participants; max, maximum; min, minimum; SD, standard deviation.

Geometric mean plot of paracetamol plasma concentration



During SS exposures of zenagamtide (oral 50 mg and s.c. 20 mg). The dashed hatched horizontal reference line represents the LLOQ. LLOQ, lower limit of quantification; SS, steady-state; s.c., subcutaneous.

Paracetamol PK parameters



At both tested SS exposures of zenagamtide (oral 50 mg and s.c. 20 mg), no delay in gastric emptying was observed

Boxes correspond to the 25th, 50th (median) and 75th percentiles; diamonds correspond to geometric means; whiskers correspond to the 5th and 95th percentiles. AUC, area under the curve; C_{max}, maximum concentration; N, total number of participants; PK, pharmacokinetic; s.c., subcutaneous; SS, steady-state.

Paracetamol PK endpoints

- ETRs [95% CIs] for paracetamol AUC_{0-60min} and AUC_{0-300min} were:
 - 0.92 [0.80, 1.07] and 1.16 [1.10, 1.21], respectively, when co-administered with **oral zenagamtide** versus baseline assessment
 - 1.11 [0.96, 1.28] and 1.30 [1.23, 1.38], respectively, when co-administered with **s.c. zenagamtide** versus baseline assessment
- ETR [95% CIs] for paracetamol C_{max} was:
 - 1.03 [0.94, 1.13] when co-administered with **oral zenagamtide** versus baseline assessment
 - 1.27 [1.14, 1.40] when co-administered with **s.c. zenagamtide** versus baseline assessment
- Median (min; max) t_{max} for paracetamol was:
 - Baseline: 45 (15; 180) min
 - S.c. zenagamtide: 47 (15; 120) mins
 - Oral zenagamtide: 60 (15; 180) mins

	n	ETR	[95% CI]
Paracetamol AUC_{0-60min} (h*µg/mL)			
Co-administered with oral zenagamtide/baseline	27	0.92	[0.80, 1.07]
Co-administered with s.c. zenagamtide/baseline	21	1.11	[0.96, 1.28]
Paracetamol AUC_{0-300min} (h*µg/mL)			
Co-administered with oral zenagamtide/baseline	27	1.16	[1.10, 1.21]
Co-administered with s.c. zenagamtide/baseline	21	1.30	[1.23, 1.38]
Paracetamol C_{max} (µg/mL)			
Co-administered with oral zenagamtide/baseline	27	1.03	[0.94, 1.13]
Co-administered with s.c. zenagamtide/baseline	21	1.27	[1.14, 1.40]
Paracetamol t_{max} (min)			
	n	Median	Min; max
Baseline	43	45	15; 180
Co-administered with oral zenagamtide	27	60	15; 180
Co-administered with s.c. zenagamtide	21	47	15; 120

For AUC and C_{max} the endpoints were logarithmically transformed and analysed using an analysis of variance model with treatment and participants as fixed effects.

AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; ETR, estimated treatment ratio; max, maximum; min, minimum; n, number of participants contributing to analysis; PK, pharmacokinetic; s.c., subcutaneous; t_{max}, time to C_{max}.

Paracetamol PK endpoints: log (body weight) as a time-dependent covariate

- Taking into account body weight as a covariate, when paracetamol was co-administered with oral and s.c. zenagamtide, gastric emptying was even more similar between baseline and zenagamtide treatment than when body weight was not used as a covariate

	n	ETR	[95% CI]
Paracetamol AUC_{0-60min} (h*µg/mL)			
Co-administered with oral zenagamtide/baseline	27	0.96	[0.72, 1.27]
Co-administered with s.c. zenagamtide/baseline	21	0.87	[0.59, 1.27]
Paracetamol AUC_{0-300min} (h*µg/mL)			
Co-administered with oral zenagamtide/baseline	27	1.05	[0.97, 1.15]
Co-administered with s.c. zenagamtide/baseline	21	1.16	[1.00, 1.36]
Paracetamol C_{max} (µg/mL)			
Co-administered with oral zenagamtide/baseline	27	0.92	[0.78, 1.09]
Co-administered with s.c. zenagamtide/baseline	21	1.07	[0.81, 1.41]

The endpoint is logarithmically transformed and analysed using an analysis of covariance model with treatment and participants as fixed effects and log (body weight) as a time-dependent covariate. Time dependency refers to the latest covariate measurement at the time of PK profile collection in the respective treatment period. AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; ETR, estimated treatment ratio; n, number of participants contributing to analysis; PK, pharmacokinetic; s.c., subcutaneous.

Safety

- The most frequently reported AEs were gastrointestinal disorders, with the most common being nausea, vomiting and constipation
- Most AEs were mild to moderate in severity and resolved by the end of the study
- Additional safety information, including safety laboratory parameters, electrocardiograms and vital signs, did not raise any new safety concerns

	Oral zenagamtide (n=42)			OC + oral zenagamtide (n=27)			s.c. zenagamtide (n=27)			OC + s.c. zenagamtide (n=21)		
	n	%	E	n	%	E	n	%	E	n	%	E
Events	39	92.9	402	16	59.3	45	20	74.1	91	13	61.9	46
Serious												
Yes		-			-			-			-	
No	39	92.9	402	16	59.3	45	20	74.1	91	13	61.9	46
Severity												
Severe	1	2.4	1	2	7.4	2		-		1	4.8	1
Moderate	19	45.2	40	2	7.4	2	5	18.5	10	3	14.3	5
Mild	38	90.5	361	13	48.1	41	20	74.1	81	13	61.9	40
Related to s.c. zenagamtide												
Probable		-			-		16	59.3	61	6	28.6	15
Possible		-			-		5	18.5	13	5	23.8	20
Unlikely		-			-		9	33.3	13	9	42.9	11
Missing	39	92.9	402	16	59.3	45	2	7.4	4		-	
Related to oral zenagamtide												
Probable	33	78.6	280	8	29.6	22	1	3.7	4		-	
Possible	23	54.8	82	6	22.2	8		-			-	
Unlikely	24	57.1	40	8	29.6	15	20	74.1	87	13	61.9	46
Missing		-			-			-			-	
Outcome												
Fatal		-			-			-			-	
Not recovered/not resolved	4	9.5	6		-		3	11.1	3	2	9.5	2
Recovering/resolving	2	4.8	2		-			-		1	4.8	2
Recovered/resolved	39	92.9	394	16	59.3	45	20	74.1	88	13	61.9	41
Unknown		-			-			-		1	4.8	1
Missing		-			-			-			-	
Events leading to withdrawal	7	16.7	13	2	7.4	2	4	14.8	10		-	

This was a combined study with OC in which the effects of zenagamtide on the PK of a combined OC were also investigated. Paracetamol was taken on day 1, day 128 and day 186. OC was taken in three 8-day periods during baseline and the oral and s.c. zenagamtide treatment periods. Oral zenagamtide was taken on days 9–135, s.c. zenagamtide was taken on days 136–192. %, percentage of participants; AE, adverse event; E, number of events; n, number of participants; OC, oral contraceptive; PK, pharmacokinetics; s.c. subcutaneous.

Conclusions



Previous studies reported GLP-1 and amylin receptor agonists can delay gastric emptying;¹ however, in another study, semaglutide 2.4 mg did not delay gastric emptying after 20 weeks of treatment²



In this study, no delay in gastric emptying was observed with zenagamtide treatment when tested at clinically relevant oral and s.c. SS exposure levels, indicating a low risk of drug-drug interactions with oral drugs taken concomitantly with zenagamtide



The safety profile of zenagamtide was as expected for GLP-1 and amylin receptor agonists,³⁻¹⁰ with no new safety concerns observed^{3,4}

GLP-1, glucagon-like peptide 1; s.c., subcutaneous; SS, steady state.

1. Lutz TA. Neuropharmacology 2025;278:110587; 2. Friedrichsen M et al. Diabetes Obes Metab 2021;23:754–762; 3. Gasiorrek A et al. Lancet 2025;406:135–148; 4. Dahl K et al. Lancet 2025;406:149–162; 5. Sanyal AJ et al. N Engl J Med 2025;392:2089–2099; 6. Perkovic V et al. N Engl J Med 2024;391:109–121; 7. Wilding JPH et al. N Engl J Med 2021;384:989–1002; 8. Lincoff AM et al. N Engl J Med 2023;389:2221–2232; 9. Kosiborod MN et al. N Engl J Med 2023;389:1069–1084; 10. Lutz TA. Appetite 2022;172:105965.