Zenagamtide, a novel, long-acting, unimolecular GLP-1 and amylin receptor agonist, does not impact the pharmacokinetics of the combined oral contraceptive, levonorgestrel/ethinylestradiol

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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 MASH[1–5]

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 AMYR[6]

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.

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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 intake[1]

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 plateau[2]

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 treatment[3]

The aim of the current study was to evaluate the effect of co-administration of zenagamtide on the PK of a combined OC pill

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.

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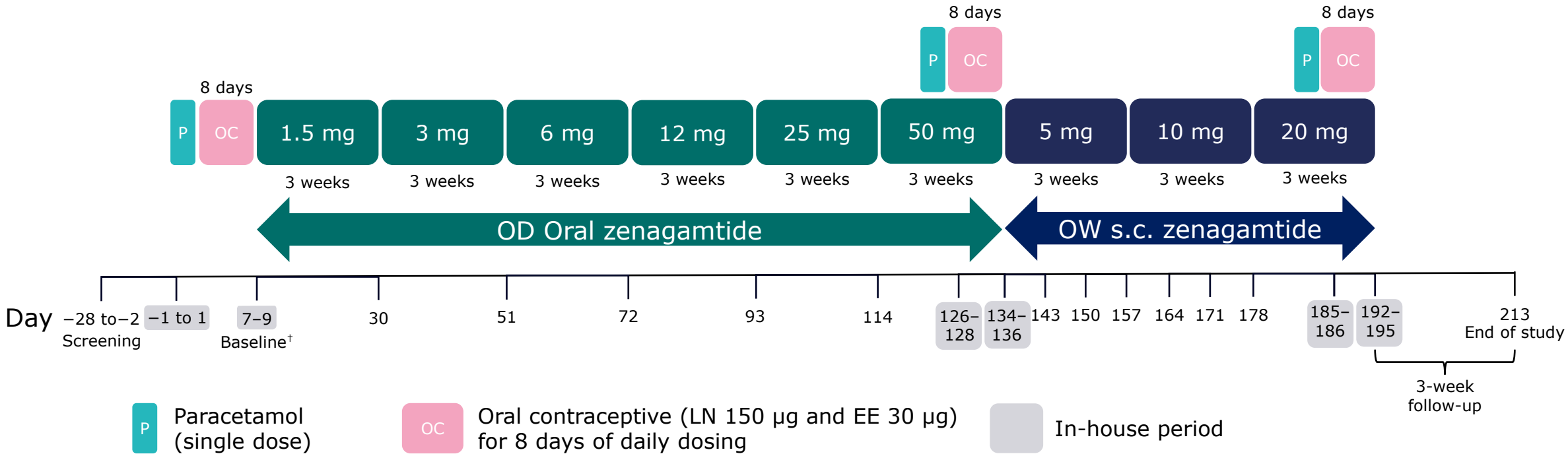
Study design

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



†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.

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Methods

Population

Female participants of non-childbearing potential aged 18–65 years with a BMI of 25.0–39.9 kg/m^2

Procedures

Participants received OD combined OC (LN 150 µg and EE 30 µg) for 8 days (baseline assessment). This was followed by OD oral dosing of zenagamtide, with dose escalation every third week to reach SS for the 50 mg dose. The oral zenagamtide treatment period was completed with administration of an 8-day treatment period of OD combined OC. This was followed by once weekly s.c. dosing of zenagamtide, with dose escalation every third week to reach SS for the 20 mg dose level. The s.c. treatment period was completed with another 8-day treatment period of OD combined OC

Outcomes

Co-primary endpoints: for both oral and s.c. zenagamtide were $AUC_{0–24h}$ for LN and EE, and were assessed at OC SS exposure during a dosing interval

Supportive secondary endpoints: C_{max} of LN and EE

'No effect' on the OC PK was defined as the 90% confidence interval for the ratio of OC PK parameters during zenagamtide SS and baseline assessment being within prespecified limits [0.80–1.25]

Statistics

Statistical analyses were based on observed data, with no imputation of missing data

AUCs were calculated using the linear trapezoidal method. Participants with an available $AUC_{0–24h}$ for LN and EE at SS from two periods (OC administered alone and OC co-administered with s.c. or oral zenagamtide) contributed to the analysis of each of the endpoints

AUC, area under the curve; BMI, body mass index; C_{max}, maximum plasma concentration; EE, ethinylestradiol; LN, levonorgestrel; OC, oral contraceptive; OD, once daily; PK, pharmacokinetics; s.c., subcutaneous; SS, steady state.

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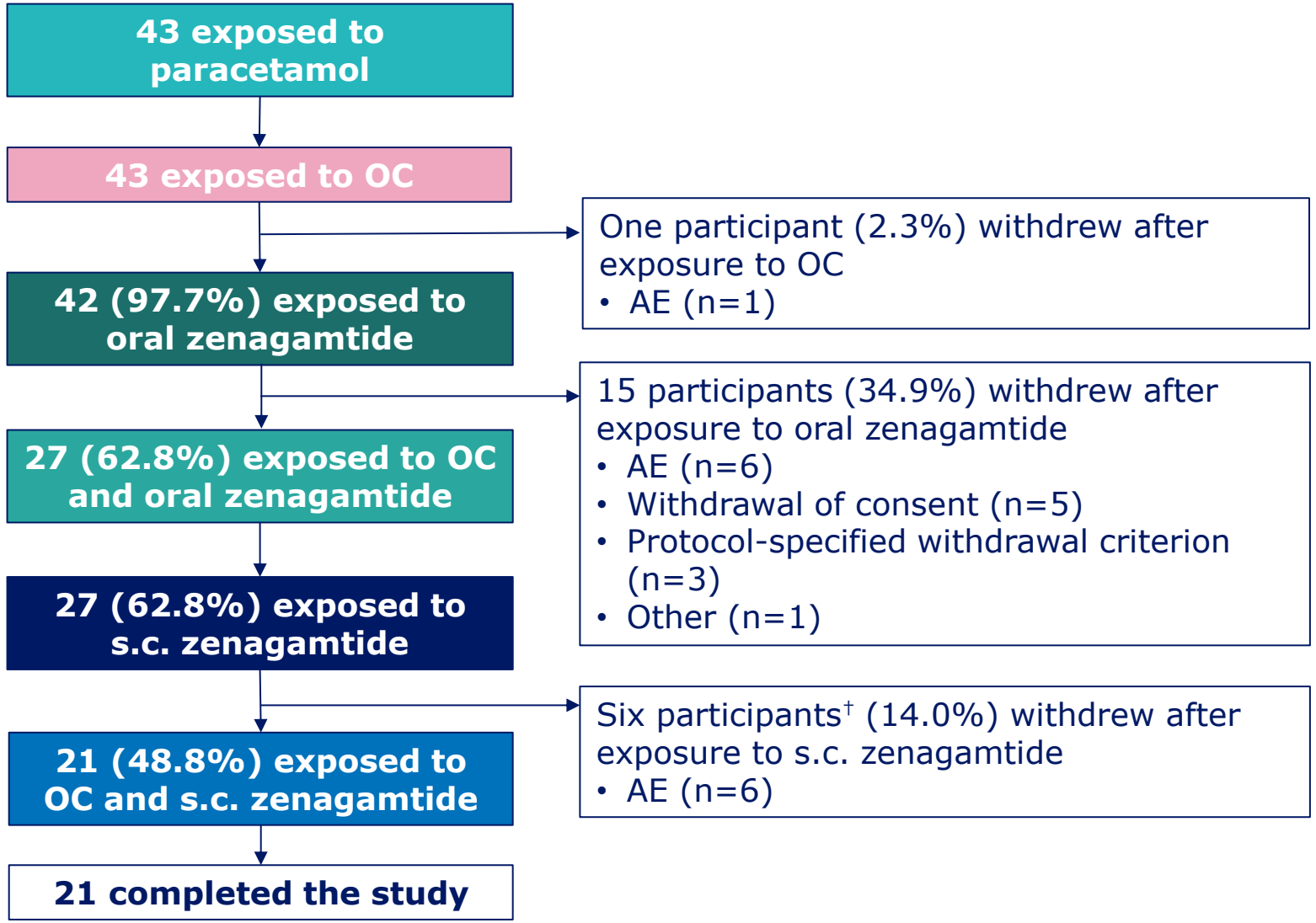
Participant flow

- 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 exposed to one dose of s.c. zenagamtide before withdrawal.
†One of these participants was withdrawn due to AEs experienced during the oral and s.c. zenagamtide dosing periods.
AE, adverse event; OC, oral contraceptive; s.c., subcutaneous.

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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/m^2

Characteristic	Total (N=43)
Race, n (%)	
White	40 (93.0)
Black or African American	1 (2.3)
Multiple	2 (4.7)
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; SD, standard deviation.

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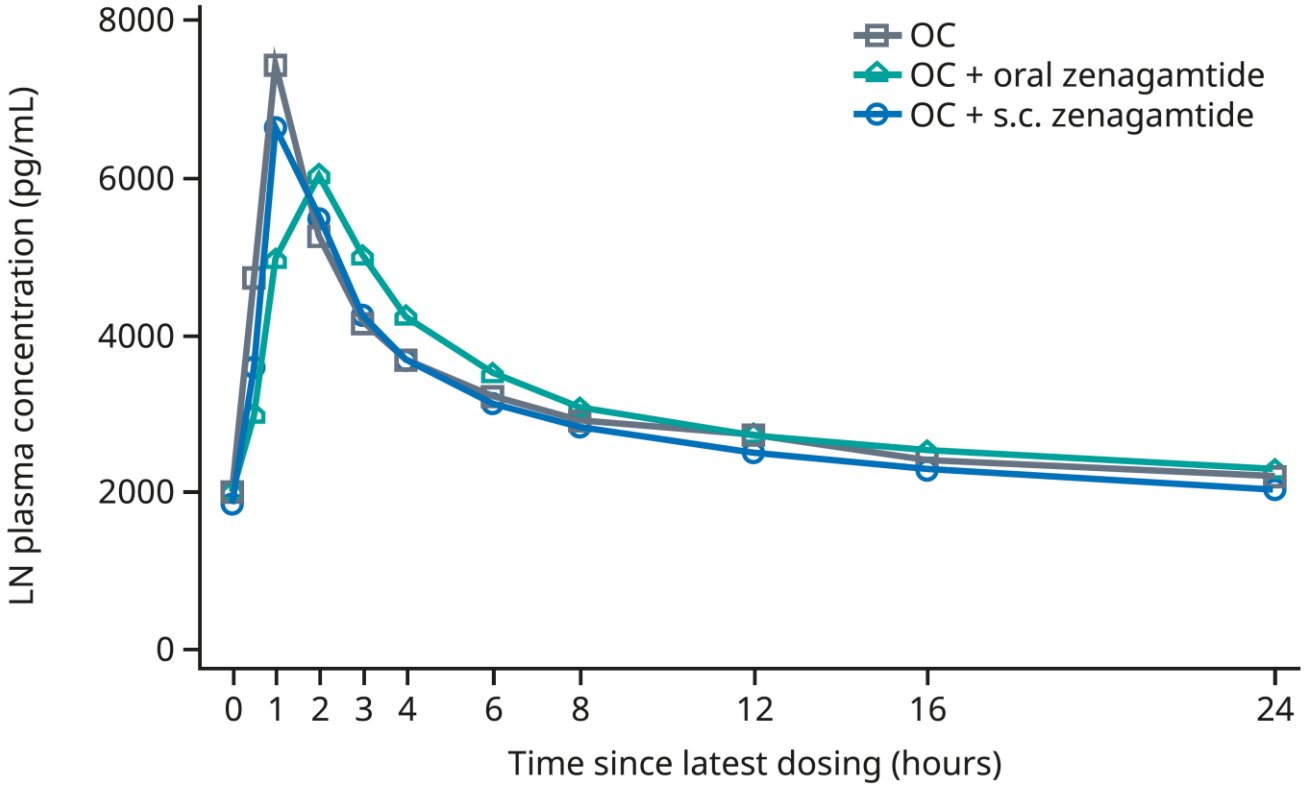
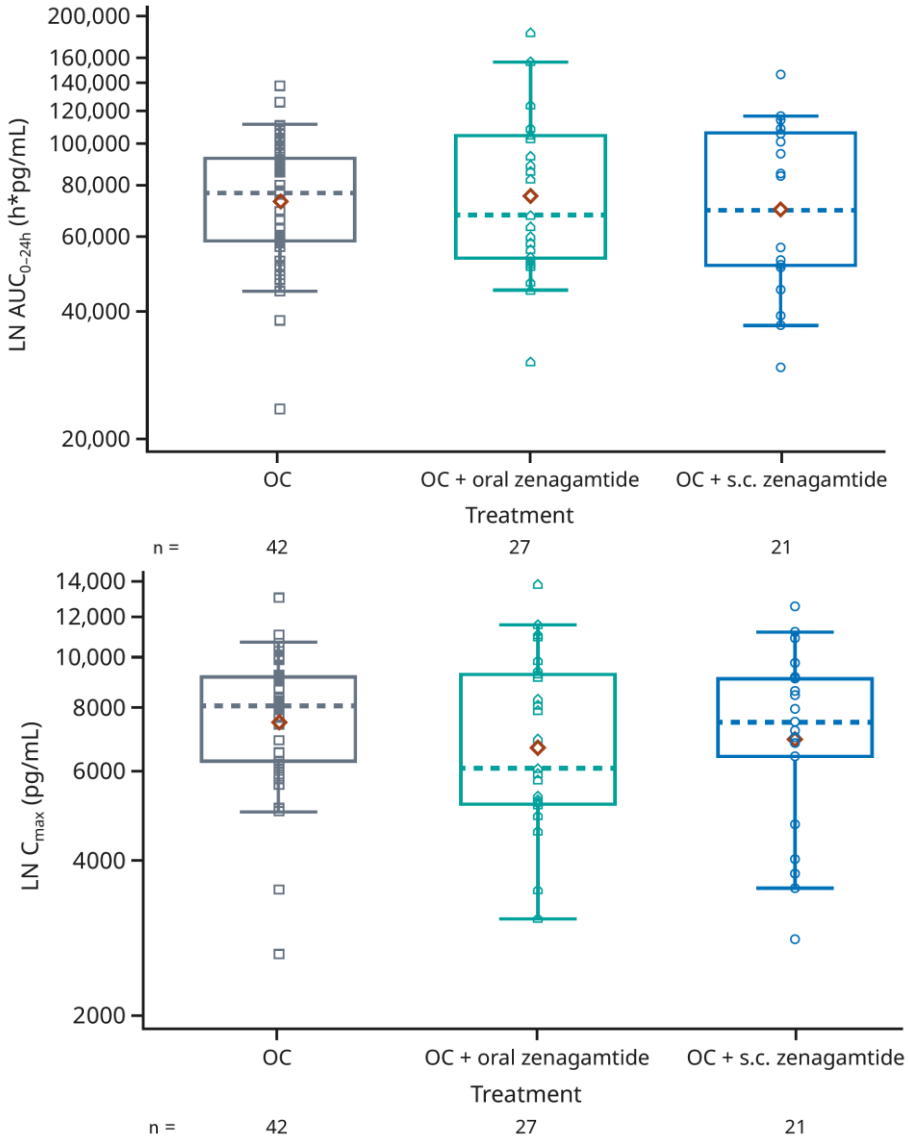
LN plasma concentrations and PK parameters





In box plots, boxes correspond to the 25th, 50th (median) and 75th percentiles; diamonds correspond to geometric means and whiskers correspond to the 5th and 95th percentiles.
AUC, area under the curve; C_{max}, maximum plasma concentration; LN, levonorgestrel; OC, oral contraceptive; PK, pharmacokinetic; s.c., subcutaneous.

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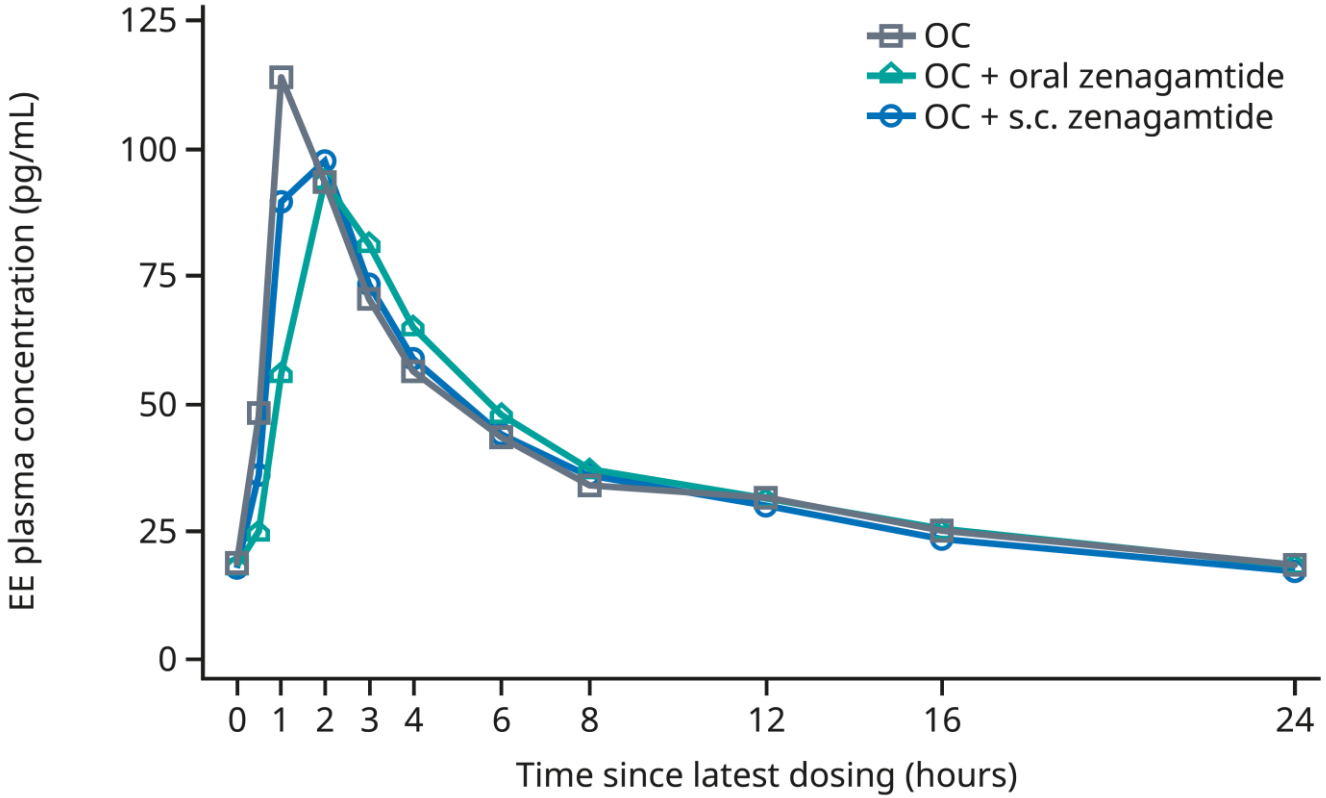
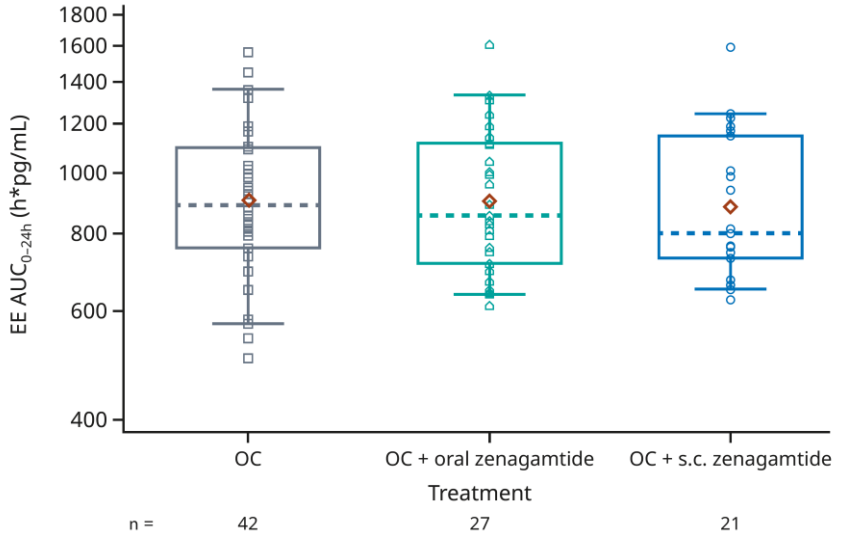
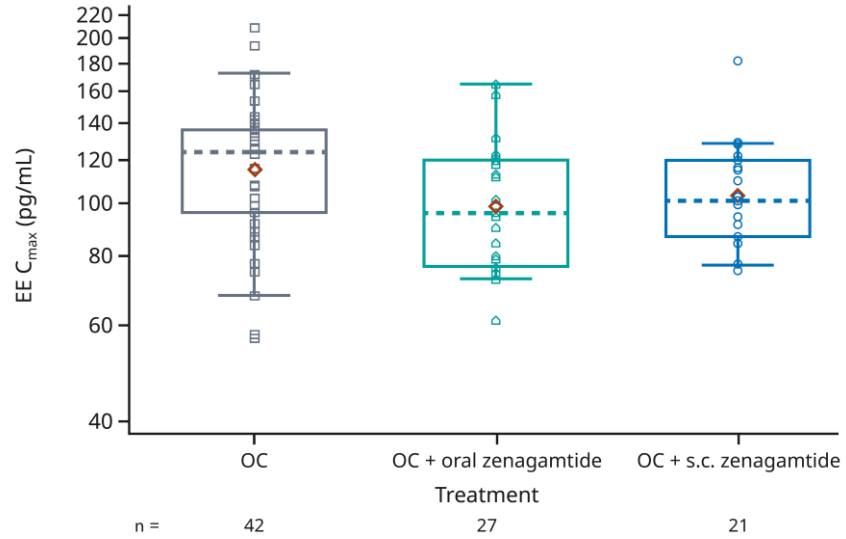
EE plasma concentration and PK parameters







In box plots, boxes correspond to the 25th, 50th (median) and 75th percentiles; diamonds correspond to geometric means and whiskers correspond to the 5th and 95th percentiles.
AUC, area under the curve; C_{max}, maximum plasma concentration; LN, levonorgestrel; OC, oral contraceptive; PK, pharmacokinetic; s.c., subcutaneous.

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LN and EE PK endpoints: ETR

The ETR and 90% CIs for the $AUC_{0–24h}$ of LN and EE were within the prespecified **'no effect'** criteria

	N	ETR	[90% CI]
LN			
$AUC_{0–24h}$ (h*pg/mL)			
Co-administered with oral zenagamtide/baseline	27	1.06	[0.99, 1.13]
Co-administered with s.c. zenagamtide/baseline	21	1.05	[0.95, 1.16]
C_{max} (pg/mL)			
Co-administered with oral zenagamtide/baseline	27	0.90	[0.82, 0.99]
Co-administered with s.c. zenagamtide/baseline	21	0.99	[0.90, 1.08]
EE			
$AUC_{0–24h}$ (h*pg/mL)			
Co-administered with oral zenagamtide/baseline	27	0.93	[0.88, 0.99]
Co-administered with s.c. zenagamtide/baseline	21	0.90	[0.83, 0.96]
C_{max} (pg/mL)			
Co-administered with oral zenagamtide/baseline	27	0.81	[0.75, 0.88]
Co-administered with s.c. zenagamtide/baseline	21	0.86	[0.79, 0.94]

AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration; EE, ethinylestradiol; ETR, estimated treatment ratio; LN, levonorgestrel; PK, pharmacokinetic; s.c., subcutaneous.

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Safety

The most frequently reported AEs were GI disorders, with the most common being nausea, vomiting and constipation

Overall, AEs were non-serious, with the vast majority being mild to moderate in severity and most were resolved by end of study

- Oral zenagamtide period: 402 events in 39 (92.9%) participants
- OC + oral zenagamtide period: 45 events in 16 (59.3%) participants
- s.c. zenagamtide period: 91 events in 20 (74.1%) participants
- OC + s.c. zenagamtide period: 46 events in 13 (61.9%) participants

Additional safety information, including laboratory parameters, electrocardiograms and vital signs did not raise any new safety concerns

AE, adverse event; GI, gastrointestinal; OC, oral contraceptive; s.c., subcutaneous.

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Conclusions

- At oral and s.c. zenagamtide SS exposures, the ‘no effect’ criteria were met for $AUC_{0–24h}$ for LN and EE, indicating no clinically relevant impact of oral and s.c. zenagamtide on OC exposure
- The safety profile of zenagamtide was as expected for GLP-1 receptor and amylin receptor agonists,[1–8] with no new safety concerns observed during co-treatment with OC and zenagamtide
- PK profiles for 50 mg oral and 20 mg s.c. zenagamtide at SS were as observed in previous studies[7,8]
- The results indicate that OC can be co-administered with zenagamtide without further need for additional contraceptive measures

AUC, area under the curve; EE, ethinylestradiol; GLP-1, glucagon-like peptide 1; LN, levonorgestrel; OC, oral contraceptive; PK, pharmacokinetic; s.c., subcutaneous; SS, steady state.

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