Effect of Oral Semaglutide on the Pharmacokinetics of Levonorgestrel and Ethinylestradiol in Healthy Postmenopausal Women and Furosemide and Rosuvastatin in Healthy Subjects

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Abstract

Background The first oral glucagon-like peptide-1 receptor agonist (GLP-1RA) comprises semaglutide co-formulated with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). Oral semaglutide may alter the pharmacokinetics of co-administered drugs via effects of semaglutide or SNAC. Two separate one-sequence crossover trials investigated the effects of oral semaglutide and SNAC on the pharmacokinetics of ethinylestradiol, levonorgestrel, furosemide and rosuvastatin.

Methods Healthy, postmenopausal women (n = 25) received once-daily combined ethinylestradiol and levonorgestrel (Trial 1) and healthy male and female subjects (n = 41) received single doses of furosemide and rosuvastatin (Trial 2), either alone, with SNAC alone or with oral semaglutide. Lack of drug–drug interaction was concluded if 90% confidence intervals (CIs) for the ratio of area under the plasma concentration–time curve (AUC) or maximum concentration (Cmax), with/without oral semaglutide, were within a pre-specified interval (0.80–1.25).

Results The AUC values of ethinylestradiol and levonorgestrel were not affected by oral semaglutide co-administration (estimated ratios [90% CI] 1.06 [1.01–1.10] and 1.06 [0.97–1.17], respectively); Cmax was not affected. The no-effect criterion was not met for furosemide or rosuvastatin for the AUC (1.28 [1.16–1.42] and 1.41 [1.24–1.60], respectively) or Cmax. SNAC alone did not affect the AUC or Cmax of ethinylestradiol, levonorgestrel or rosuvastatin; the Cmax of furosemide was slightly decreased. Adverse events were similar to those previously observed for GLP-1RAs (both trials).

Conclusion Co-administration with oral semaglutide did not affect the pharmacokinetics of ethinylestradiol or levonorgestrel. There was a small increase in exposure of furosemide and rosuvastatin; however, these increases are not expected to be of clinical relevance.

Clinical Trial Registration Numbers NCT02845219 and NCT03010475.

Key Points

The victim drugs ethinylestradiol, levonorgestrel, furosemide and rosuvastatin are commonly used drugs in patients with type 2 diabetes.

Oral semaglutide had no statistically significant effect on the exposure of ethinylestradiol or levonorgestrel but resulted in a small increase in the exposure of furosemide and rosuvastatin, which is not expected to be of clinical relevance.

Oral semaglutide was found to be well-tolerated in combination with these drugs and no new safety issues were identified.
1 Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an effective treatment option for type 2 diabetes (T2D). Several GLP-1RAs are currently marketed, all of which are administered by subcutaneous injection [1]. Once-weekly subcutaneous administration of the GLP-1 analogue semaglutide has been shown to improve glycaemic control and reduce body weight in patients with T2D [2–6]. Semaglutide has 94% sequence homology to native human GLP-1 [7]. Structural differences between native GLP-1 and semaglutide include amino acid substitutions at position 8 (alanine to α-aminoisobutyric acid) and position 34 (lysine to arginine), and acylation of the lysine in position 26 with a spacer and C-18 fatty diacid chain [8]. The substitution at position 8 makes semaglutide less susceptible to degradation by dipeptidyl peptidase-4 [9], while the spacer and fatty diacid mediate strong binding to albumin [10].

Oral semaglutide is a novel tablet comprising the active pharmaceutical ingredient (API) semaglutide co-formulated with an absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC; 300 mg) [11], which protects semaglutide against enzymatic degradation through a localised increase in pH and transiently enhances absorption across the gastric epithelium via the transcellular route [12, 13]. Oral administration of GLP-1-based therapies offers the potential for earlier treatment and may improve patient acceptance and adherence for more patients with T2D [14]. In clinical trials, oral semaglutide has demonstrated substantial dose-dependent lowering of both glycated haemoglobin (HbA1c) and body weight [15–17], with a safety profile in line with other GLP-1RAs [15, 18].

In previous studies, there was no apparent effect of renal impairment on the pharmacokinetics of oral semaglutide [19], and semaglutide plasma exposure appeared similar across hepatic function groups in subjects with hepatic impairment [20]. In an absorption, metabolism and excretion trial with subcutaneous semaglutide, it was shown that semaglutide is metabolised prior to excretion, with semaglutide-related material excreted in both urine (only 3% elimination of intact semaglutide) and faeces [7]. In addition, cytochrome P450 (CYP) enzymes and transporters are not expected to be inhibited or induced by semaglutide [9].

Like other GLP-1RAs [21], semaglutide administration results in a small delay in gastric emptying during the first hour after a meal [22]. Oral semaglutide may potentially alter the pharmacokinetics of concomitantly administered drugs (victim drugs) via the effect on gastric emptying (as has been shown for other GLP-1RAs [21]) or via the effects of the absorption enhancer SNAC, although recent drug–drug interaction (DDI) studies found that oral semaglutide had no clinically meaningful effect on the exposure of four victim drugs (lisinopril, warfarin, digoxin and metformin) commonly used in patients with T2D [23].

Metabolism of ethinylestradiol and levonorgestrel occurs mainly in the liver but also in the gastrointestinal tract [24] via CYP enzymes, particularly by CYP3A4, which is expressed in the liver and intestine [25]. In addition, ethinylestradiol is metabolised by conjugation by uridine diphosphate glucuronosyltransferase (UGT) 1A1 [26] and oestrogen sulfotransferase 1E1 [27]. As in vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, or to inhibit drug transporters [9], and other in vitro studies demonstrated that SNAC does not inhibit or induce any of the CYP enzymes or inhibit UGT enzymes [28], the risk of DDIs between oral semaglutide and ethinylestradiol and levonorgestrel is considered low. However, the intended population to be treated with oral semaglutide is likely to include women of child-bearing potential receiving oral contraception. Therefore, in vivo confirmation in women is required to provide evidence that the systemic exposure of ethinylestriadiol or levonorgestrel will not be impacted by co-administration of oral semaglutide.

Furosemide is a loop diuretic used to treat oedema associated with cardiac, renal and hepatic failure. The bioavailability of furosemide is poor when administered orally, and can vary greatly between individuals [29]. Rosuvastatin is a statin (HMG-CoA reductase inhibitor) used for the treatment of dyslipidaemia. The bioavailability of orally administered rosuvastatin is approximately 20% [30, 31]. In vitro data suggest that SNAC may inhibit uptake and efflux transporters, such as the breast cancer resistance protein (BCRP) and organic-anion-transporter (OAT) 1 and/or 3 and OAT polypeptide OATP1B1, potentially leading to increased plasma levels of certain transporter substrates [32]. US Food and Drug Administration (FDA) guidelines list furosemide as a suitable victim drug to test potential DDIs for OAT1 and/or OAT3 and rosuvastatin as a suitable victim drug to test potential DDIs for BCRP, OAT1 and/or OAT3 and OATP1B1 [33].

Here, we report the results of two trials that were conducted to investigate the effects of oral semaglutide on the pharmacokinetics of a combined oral contraceptive (OC) containing ethinylestradiol and levonorgestrel (Trial 1, NCT02845219 [34]), and furosemide and rosuvastatin (Trial 2, NCT03010475 [35]).

2 Methods

2.1 Trial Design and Populations

Relevant Ethics Committees (Trial 1: Landesamt für Gesundheit und Soziales und Geschäftsstelle der Ethikkommission
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2.2 Treatments

In each trial, the victim drug was administered in three periods: (1) alone; (2) with SNAC alone; or (3) with oral semaglutide. Oral semaglutide is a co-formulation of the API semaglutide and the absorption enhancer SNAC 300 mg.

2.2.1 Trial 1 (Ethinylestradiol/Levonorgestrel)

Subjects received a once-daily OC (Microgynon® containing ethinylestradiol 0.03 mg and levonorgestrel 0.15 mg) in three 8-day periods. In the first period, the OC was administered alone (OC); in the second period, the OC was administered concomitantly with a tablet of SNAC 300 mg (OC + SNAC) and SNAC once-daily dosing was continued for 8 days to ensure SNAC exposure during the OC pharmacokinetic sampling period. Once-daily treatment with oral semaglutide was then initiated and subjects were dose-escalated weekly from 3 to 7 mg, and then from 7 to 14 mg. Subjects were then maintained on oral semaglutide 14 mg for 4 weeks to reach semaglutide steady state before the start of the third treatment period, where the OC was administered concomitantly with oral semaglutide (OC + oral semaglutide). Each treatment period was followed by 10 days of ethinylestradiol and levonorgestrel pharmacokinetic sampling (Fig. 1a). Oral semaglutide administration was continued to maintain exposure during the 10 days of ethinylestradiol and levonorgestrel pharmacokinetic sampling.

2.2.2 Trial 2 (Furosemide/Rosuvastatin)

In Trial 2, furosemide 40 mg and rosuvastatin 20 mg were administered in three periods, as separate single doses on consecutive days, i.e. with a 24-h washout period in between each dose. In the first period, furosemide and rosuvastatin were administered alone (without perpetrator drug). In the second period, furosemide and rosuvastatin were co-administered with SNAC alone was also included in order to differentiate between the possible effects of semaglutide and SNAC (Fig. 1).

Both trials had an open-label, one-sequence, crossover trial design. In Trial 1, postmenopausal women (aged ≥ 45 years with ≥ 12 consecutive months since last spontaneous menstrual bleeding) were included in order to avoid any potential effect on pharmacokinetics of levonorgestrel and ethinylestradiol caused by physiological hormonal fluctuations seen in women of childbearing potential. Trial 2 included healthy male and female subjects aged 18–65 years. In both trials, body mass index was required to be 20.0–29.9 kg/m². Subjects were considered generally healthy based on medical history, physical examination, electrocardiogram and clinical laboratory tests. Full exclusion criteria are listed in the Electronic Supplementary Material (ESM; Online Resource 1, Table S1).
was made at steady state conditions with oral semaglutide 14 mg and for SNAC in the OC + SNAC and furosemide/ rosvastatin + SNAC periods, respectively (Fig. 1a, b).

### 2.3 Endpoints

The primary endpoints were area under the plasma concentration–time curve (AUC) from time 0 to 24 h at steady state (AUC\(_{0-24,SS}\)) for ethinylestradiol (AUC\(_{0-24,EE,SS}\)) and levonorgestrel (AUC\(_{0-24,LN,SS}\)) (Trial 1) and AUC from time zero to infinity (AUC\(_{0-\infty}\)) for single doses (AUC\(_{0-\infty,SD}\)) of furosemide (AUC\(_{0-\infty,furo,SD}\)) and rosvastatin (AUC\(_{0-\infty,rosu,SD}\)) (Trial 2). Secondary endpoints were maximum concentration (\(C_{max}\)), time to \(C_{max}\) (\(t_{max}\)) and terminal half-life (\(t_{1/2}\)) for all four victim drugs.

### 2.4 Analytical and Statistical Methods

#### 2.4.1 Pharmacokinetic Assessments

#### 2.4.1.1 Bioanalysis

The methods for semaglutide and SNAC bioanalysis have previously been described [20]. Validated liquid chromatography mass spectrometry (LC-MS/MS) assays were used to investigate plasma concentrations of the four victim drugs: ethinylestradiol, levonorgestrel, furosemide and rosvastatin. Full details are described in ESM Online Resource 1, Table S2.

Pre-dose values that were below the lower limit of quantification (LLOQ) were set to zero. Intermediate samples (after dosing and before the last quantifiable observation) were set to LLOQ/2. LLOQ values obtained after the last
quantifiable observation were imputed based on $t_{1/2}$. If $t_{1/2}$ was unavailable, then the first value after the last quantifiable observation was set to LLOQ/2 and the remaining values were set to zero.

### 2.4.1.2 Determination of Sample Size

Based on 21 subjects completing the trial, Trial 1 was calculated to have an overall combined statistical power of at least 80% of concluding no effect for the four endpoints (i.e. $AUC_{0-24,SS}$ and $C_{max}$ at steady state [$C_{max,SS}$] for both ethinylestradiol and levonorgestrel), assuming $AUC$ and $C_{max}$ ratios of 0.95 when comparing ethinylestradiol/levonorgestrel co-administered with oral semaglutide versus ethinylestradiol/levonorgestrel alone. The within-subject standard deviations (SDs) for ethinylestradiol were 0.149 and 0.215 for log($AUC_{0-24,SS}$) and log($C_{max,SS}$), respectively. The within-subject SDs for levonorgestrel were 0.165 and 0.236 for log($AUC_{0-24,SS}$) and log($C_{max,SS}$), respectively. Due to the long duration of the trial with no replacement of subjects in case of withdrawals, 25 subjects were included.

Based on 36 subjects completing the trial, Trial 2 was calculated to have an overall combined statistical power of 80% of concluding no effect for the four endpoints (i.e. $AUC_{0-\infty,SD}$ and $C_{max}$ for single doses [$C_{max,SD}$] for both furosemide and rosvastatin), assuming $AUC$ and $C_{max}$ ratios of 0.95 when comparing furosemide/rosvastatin co-administered with oral semaglutide versus furosemide/rosvastatin alone. The within-subject SDs for furosemide were estimated to be 0.217 and 0.215 for log($AUC_{0-\infty,SD}$) and log($C_{max,SD}$), respectively. The within-subject SDs for rosvastatin were estimated to be 0.191 and 0.244 for log($AUC_{0-\infty,SD}$) and log($C_{max,SD}$), respectively. Allowing up to 12% dropout, 41 subjects were included. During the trial, blood samples from six subjects for rosvastatin pharmacokinetic analysis were accidentally thawed during shipment, making the assessment of rosvastatin pharmacokinetic endpoints impossible for these subjects. In addition, two subjects were withdrawn from the trial, resulting in 33 subjects with evaluable data for the rosvastatin pharmacokinetic endpoints. The loss in statistical power was considered to be acceptable and therefore no extra subjects were enrolled in the trial. The statistical power in both trials was calculated using two and therefore no extra subjects were enrolled in the trial. The loss in statistical power was considered to be acceptable for the rosuvastatin pharmacokinetic endpoints.

### 2.4.1.3 Determination of Sample Size

In both trials, the full analysis set and safety analysis set included all subjects who were exposed to at least one dose of a trial product.

### 3 Results

#### 3.1 Demographics

In Trial 1, 25 healthy postmenopausal women were exposed to the trial products and completed the trial. In Trial 2, 41 healthy male and female subjects were exposed to the trial product and two withdrew consent after exposure—one subject withdrew after administration of rosvastatin alone and one subject withdrew after starting oral semaglutide treatment; neither withdrawal was due to any adverse events (AEs). The remaining 39 subjects completed the trial and all 41 subjects were included in the full and safety analysis sets. Demographics and baseline characteristics are presented in Table 1.

#### 3.2 Pharmacokinetics

##### 3.2.1 Trial 1 (Ethinylestradiol/Levonorgestrel)

Mean concentration–time profiles for ethinylestradiol and levonorgestrel for the three treatment periods (OC, OC + SNAC, OC + oral semaglutide) are presented in Fig. 2a, b.

##### 3.2.1.1 Ethinylestradiol/Levonorgestrel

The estimated treatment ratio of $AUC_{0-24,SS}$ for ethinylestradiol was 1.06 and the 90% CI (1.01–1.10) was within the pre-specified ‘no effect’ interval. The estimated ratio of $AUC_{0-\infty,SS}$ for levonorgestrel was 1.06 and the 90% CI (0.97–1.17) was also within the pre-specified ‘no effect’ interval. Similarly, the 90% CIs for the estimated ratios of $C_{max}$ for ethinylestradiol and levonorgestrel were within the pre-specified interval (Fig. 3a), indicating that co-administration of oral semaglutide had no effect on the exposure of ethinylestradiol or levonorgestrel. Other secondary endpoints, including $t_{1/2}$ and $t_{max}$, were similar for all three treatment periods (Tables 2 and 3).

##### 3.2.1.2 Semaglutide and Sodium N-(8-[2-Hydroxybenzoyl]Amino) Caprylate (SNAC)

Pharmacokinetic parameters for semaglutide and SNAC are shown in ESM Online Resource 1, Table S3a. The geometric mean $C_{max}$ of semaglutide was 25.7 nmol/L.
3.2.2 Trial 2 (Furosemide/Rosuvastatin)

Mean concentration–time profiles for furosemide and rosuvastatin with/without oral semaglutide are shown in Fig. 2c, d.

3.2.2.1 Furosemide The estimated ratio for the $AUC_{0-\infty}$ of furosemide co-administered with oral semaglutide compared with the $AUC_{0-\infty}$ of furosemide alone was 1.28 and the 90% CI (1.16–1.42) was not within the pre-specified ‘no effect’ interval. Additionally, the ‘no effect’ criterion was not met for the $C_{\text{max}}$ of furosemide (Fig. 3b). When co-administered with SNAC alone, there was no effect on the $AUC_{0-\infty}$ of single-dose furosemide while the $C_{\text{max}}$ was slightly decreased. The median $t_{\text{max}}$ was similar for furosemide when dosed alone and when co-administered with SNAC alone, but slightly later when co-administered with oral semaglutide. The $t_{1/2}$ of furosemide was similar for all three treatment periods (Table 4).

3.2.2.2 Rosuvastatin When co-administered with oral semaglutide, the estimated ratio for $AUC_{0-\infty}$ of rosuvastatin was 1.41 and the 90% CI (1.24–1.60) was not within the pre-specified interval. Additionally, the ‘no effect’ criterion was not met for the $C_{\text{max}}$ of rosuvastatin (Fig. 3b). The $AUC_{0-\infty}$ and $C_{\text{max}}$ values of rosuvastatin were not affected by co-administration of SNAC alone (Fig. 3b). The median $t_{\text{max}}$ was similar for rosuvastatin when dosed alone and when co-administered with SNAC alone, but slightly later when co-administered with oral semaglutide. The $t_{1/2}$ of rosuvastatin was similar for all three treatment periods (Table 5).

3.2.2.3 Semaglutide and SNAC Pharmacokinetic parameters for semaglutide and SNAC are shown in ESM Online Resource 1, Table S3b. The geometric mean $C_{\text{max}}$ of semaglutide was 28.4 nmol/L.

3.3 Safety and Tolerability

3.3.1 Trial 1 (Ethinylestradiol/Levonorgestrel)

A total of 24 subjects had at least one AE during Trial 1. There were no deaths or serious AEs, no severe AEs and no AEs leading to withdrawal from the trial. An overview of treatment-emergent AEs is shown in Table 6. The most commonly reported AEs were gastrointestinal disorders, occurring in 80% (20/25) of subjects, primarily nausea, which occurred in 64% (16/25) of subjects. Most gastrointestinal-related AEs occurred during the dose-escalation period of oral semaglutide treatment and continued during co-administration with the OC. Reproductive system and breast disorders were the second most commonly reported AEs by organ class, reported in 68% (17/25) of subjects (Table 6), of which vaginal haemorrhaging was the most common event, occurring in 64% (16/25) of subjects. The onset of vaginal haemorrhaging occurred in all three OC treatment periods, with more subjects having vaginal haemorrhaging during the OC + SNAC [60% (15/25)] and OC + oral semaglutide [44% (11/25)] treatment periods than with OC alone [12% (3/25)]. Metabolism and nutritional disorders were the third most commonly reported AEs, mainly in the form of decreased appetite, occurring in 80% (20/25) of subjects. In addition, seven AEs relating to laboratory abnormalities of increased liver enzymes were reported in five subjects during OC administration; six events were related to alanine transaminase (ALT), one event was related to aspartate transaminase (AST), and one subject had both AST and ALT elevation. All seven events were moderate in severity and none lasted more than 9 days. Overall, mean levels of both AST and ALT remained within the normal ranges and returned to normal at the end of each OC period.

Table 1 Demographics and baseline characteristics

| Demographic/characteristic | Trial 1 (ethinylestradiol/levonorgestrel) ($n = 25$) | Trial 2 (furosemide/rosuvastatin) ($n = 41$) |
|----------------------------|-----------------------------------------------|-----------------------------------------------|
| Mean age, years (min; max) | 62 (50; 75)                                   | 39 (18; 65)                                   |
| Sex, n (%)                 | Female 25 (100)                               | Male 10 (24.4)                                |
|                           | Male 0 (0)                                    | Male 31 (75.6)                                |
| Race, n (%)                | White 25 (100)                                | Black or African American 0 (0)                |
|                           | Other 0                                       | Other 2 (4.9)                                 |
| Mean body weight, kg (min; max) | 65.5 (55.8; 77.8)                          | 77.0 (50.7; 95.7)                             |
| Mean BMI, kg/m² (min; max) | 24.1 (21.7; 28.8)                             | 25.0 (20.1; 29.8)                             |
| Mean HbA1c, % (min; max)   | 5.6 (5.3; 6.2)                                | 5.4 (4.7; 6.1)                                |

$BMI$ body mass index, $HbA1c$, glycated haemoglobin, $max$ maximum, $min$ minimum

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3.3.2 Trial 2 (Furosemide/Rosuvastatin)

A total of 37 subjects (90.2%) had at least one AE during Trial 2. AEs occurred primarily during oral semaglutide treatment, including the dose-escalation period. There were no deaths and no serious AEs reported in this trial. An overview of treatment-emergent AEs is shown in Table 6. Similar to Trial 1, the majority of AEs were gastrointestinal disorders, occurring in 59% (24/41) of subjects, and nausea was reported in 29% (12/41) of subjects. There was one severe event of abdominal pain reported during the oral semaglutide alone period. Nervous system disorders, mainly
headache, were the second most commonly reported AEs by organ class. There was one case of abnormally increased blood creatinine phosphokinase, which was reported as mild. The increase in blood creatinine kinase was most likely caused by physical exercise and was not considered to be clinically relevant.

4 Discussion

The main purpose of these studies was to assess the effect of oral semaglutide on the pharmacokinetics of ethinylestradiol, levonorgestrel, furosemide and rosuvastatin. In addition, the potential impact of the absorption enhancer SNAC alone was tested to differentiate between the effects caused by semaglutide and by SNAC. In Trial 1, no statistically significant pharmacokinetic interaction was observed when oral semaglutide was co-administered with ethinylestradiol or levonorgestrel, suggesting that oral semaglutide does not have an impact on the contraceptive effect. In line with these findings, a previous trial found that once-weekly subcutaneous semaglutide did not affect exposure of ethinylestradiol and levonorgestrel to any clinically relevant degree, even though a 20% increase in levonorgestrel AUC was observed [9].

In Trial 2, co-administration of oral semaglutide with a single dose of furosemide resulted in a 28% increase in total furosemide exposure and a 34% decrease in the maximum furosemide concentration. There was no effect on the AUC when furosemide was co-administered with SNAC, but the $C_{\text{max}}$ was slightly decreased. Co-administration of oral semaglutide with a single dose of rosuvastatin resulted in a 41% increase in total rosuvastatin exposure (and 10% increase in

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maximum rosvastatin concentration); however, there was no effect on exposure or $C_{\text{max}}$ when rosvastatin was co-administered with SNAC. Consequently, the effects observed when furosemide and rosvastatin were co-administered with oral semaglutide should not be attributed to effects of SNAC on the BCRP, OAT1 and/or OAT3 and OATP1B1 transporters. Rather, they may be related to the GLP-1RA component of oral semaglutide, potentially due to a small delay in gastric emptying, a known effect of GLP-1RAs that may influence the rate and extent of absorption of co-administered drugs [22]. Orally administered furosemide has poor bioavailability (47%) and absorption of furosemide can be inconsistent [29, 41]. The delay in gastric emptying caused by the GLP-1RA component of oral semaglutide could therefore explain the decrease in $C_{\text{max}}$ and the increased total exposure with furosemide. The clinical relevance of the pharmacokinetic changes observed for furosemide and rosvastatin have not been investigated in this trial; however, furosemide has a high variability in bioavailability between individuals [29, 42] and the dosing is generally adjusted individually in the clinic. In addition, furosemide has a broad therapeutic index and is generally well-tolerated. Similarly, rosvastatin is generally well-tolerated [43, 44], and a similar increase in rosvastatin exposure has previously been reported, concluding no clinical relevance [45]. Based on this evidence, we do not believe the results observed in the present trial with regards to furosemide and rosvastatin are of any clinical relevance.

In Trials 1 and 2, a clinically relevant exposure of semaglutide was achieved as the $C_{\text{max}}$ of semaglutide was similar to that seen with once-weekly subcutaneous semaglutide in patients with T2D [46].

--- lower limit of quantification (0.1 ng/mL)

Fig. 2 (continued)
In both trials, the safety and tolerability profile of oral semaglutide was consistent with previous trials and with the class effects of GLP-1RAs [16–19, 47–50]. A higher proportion of subjects experienced gastrointestinal AEs in the present studies than in the phase II dose-finding trial, which could be attributed to a faster dose-escalation regimen [15]. In Trial 1, vaginal haemorrhaging was a commonly reported AE; however, this is known to occur in postmenopausal women receiving hormone replacement therapy and was therefore likely related to OC dosing [51, 52]. Moderate and transient ALT and AST elevations were noted in five subjects. As the trial was not designed to assess the increased values of ALT and AST, it was not possible to distinguish between an effect of repeated OC treatments and the effect of co-administration of OC and oral semaglutide. However, a link between OC use and increased liver parameters has been proposed [53].

\[ \text{Fig. 3} \text{ Estimated AUC and } C_{\text{max}} \text{ ratios (with 90% CI) for ethinylestradiol and levonorgestrel (a) and furosemide and rosuvastatin (b) with co-administration of oral semaglutide or SNAC alone. No effect is confirmed if the 90% CI is entirely within the pre-specified interval of 0.80–1.25. The ANOVA model based on the log-transformed endpoint as dependent variable and subject and period (with/without co-administration of oral semaglutide or SNAC alone) as fixed factors. Oral semaglutide is the formulation of the active pharmaceutical ingredient semaglutide and the absorption enhancer SNAC 300 mg. ANOVA analysis of variance, AUC area under the plasma concentration–time curve, AUC_{0-24} AUC from time zero to 24 h, AUC_{0-inf} AUC from time zero to infinity, CI confidence interval, } C_{\text{max}} \text{ maximum concentration, SNAC sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.} \]
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A potential limitation of these trials is that they had a one-sequence crossover design and differences in observation/exposure periods could make it difficult to compare safety and tolerability profiles between treatment periods. The trial population of healthy subjects differs from the target population for oral semaglutide; nevertheless, the criteria for participant selection were in accordance with the FDA and EMA guidelines for DDI clinical trials [39, 40] and the use of healthy subjects prevents the potential confounding effect of concomitant medications and co-morbidities.

| Table 2 | Pharmacokinetic endpoints for ethinylestradiol (steady state) either alone or after co-administration with oral semaglutide or sodium N-(8-[2-hydroxybenzoyl] amino) caprylate alone |
| Parameters | OC alone (n = 25) | OC + SNAC alone (n = 25) | OC + oral semaglutide (n = 25) |
| AUC<sub>0-24</sub>, pg h/mL | | | |
| Geometric mean (CV) | 783.1 (23.5) | 817.8 (17.5) | 826.9 (22.5) |
| Arithmetic mean (SD) | 803.3 (183.8) | 829.7 (144.9) | 846.1 (181.6) |
| C<sub>max</sub>, pg/mL | | | |
| Geometric mean (CV) | 102.8 (24.6) | 115.9 (17.4) | 99.9 (22.7) |
| Arithmetic mean (SD) | 105.7 (25.7) | 117.6 (21.2) | 102.2 (21.4) |
| t<sub>1/2</sub>, h | | | |
| Geometric mean (CV) | 19.1 (17.5) | 19.2 (13.0) | 20.5 (17.2) |
| Arithmetic mean (SD) | 19.4 (3.3) | 19.3 (2.6) | 20.8 (3.6) |
| t<sub>max</sub>, h, median (min; max) | 1.0 (1.0; 2.0) | 1.0 (1.0; 1.0) | 1.0 (1.0; 3.0) |

Oral semaglutide is the formulation of the active pharmaceutical ingredient semaglutide and the absorption enhancer SNAC 300 mg

AUC<sub>0-24</sub> area under the plasma concentration–time curve from time zero to 24 h, C<sub>max</sub> maximum concentration, CV coefficient of variation, max maximum, min minimum, OC combined oral contraceptive, SD standard deviation, SNAC sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, t<sub>1/2</sub> terminal half-life, t<sub>max</sub> time to reach maximum concentration

| Table 3 | Pharmacokinetic endpoints for levonorgestrel (steady state) either alone or after co-administration with oral semaglutide or sodium N-(8-[2-hydroxybenzoyl] amino) caprylate alone |
| Parameters | OC alone (n = 25) | OC + SNAC alone (n = 25) | OC + oral semaglutide (n = 25) |
| AUC<sub>0-24</sub>, pg h/mL | | | |
| Geometric mean (CV) | 77,662.9 (30.4) | 87,508.9 (26.9) | 82,478.3 (34.1) |
| Arithmetic mean (SD) | 81,045.3 (24,564.9) | 90,516.1 (24,534.6) | 86,845.2 (28,435.1) |
| C<sub>max</sub>, pg/mL | | | |
| Geometric mean (CV) | 7974.6 (28.2) | 8614.5 (21.1) | 7610.3 (27.2) |
| Arithmetic mean (SD) | 8251.6 (2081.4) | 8795.2 (1819.2) | 7858.0 (1927.8) |
| t<sub>1/2</sub>, h | | | |
| Geometric mean (CV) | 32.8 (15.4) | 33.4 (15.6) | 31.9 (17.2) |
| Arithmetic mean (SD) | 33.2 (5.0) | 33.8 (5.2) | 32.3 (5.5) |
| t<sub>max</sub>, h, median (min; max) | 1.0 (0.5; 4.0) | 1.0 (1.0; 1.0) | 1.0 (0.5; 1.0) |

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AUC<sub>0-24</sub> area under the plasma concentration–time curve from time zero to 24 h, C<sub>max</sub> maximum concentration, CV coefficient of variation, max maximum, min minimum, OC combined oral contraceptive, SD standard deviation, SNAC sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, t<sub>1/2</sub> terminal half-life, t<sub>max</sub> time to reach maximum concentration
Table 4 Pharmacokinetic endpoints for furosemide (single dose) either alone or after co-administration with oral semaglutide or sodium N-(8-[2-hydroxybenzoyl] amino) caprylate alone

| Parameters | Effect of oral semaglutide | Effect of SNAC |
|------------|----------------------------|----------------|
|            | Furosemide alone (n = 39)  | Furosemide + oral semaglutide (n = 39) | Furosemide alone (n = 40) | Furosemide + SNAC alone (n = 40) |
| **AUC<sub>0-∞</sub>, ng·h/mL** | | | | |
| Geometric mean (CV) | 1864.2 (25.0) | 2393.8 (32.2) | 1842.8 (25.8) | 1816.3 (33.2) |
| Arithmetic mean (SD) | 1918.8 (461.1) | 2517.1 (874.3) | 1900.2 (470.1) | 1912.0 (631.1) |
| **C<sub>max</sub>, ng/mL** | | | | |
| Geometric mean (CV) | 847.2 (54.2) | 556.9 (67.6) | 821.9 (57.8) | 743.7 (68.5) |
| Arithmetic mean (SD) | 959.7 (505.0) | 665.6 (405.4) | 942.0 (510.9) | 890.1 (532.8) |
| **t<sub>½</sub>, h** | | | | |
| Geometric mean (CV) | 4.4 (42.2) | 4.2 (81.1)<sup>a</sup> | 4.4 (41.7) | 4.3 (44.9)<sup>b</sup> |
| Arithmetic mean (SD) | 4.8 (2.3) | 5.9 (8.0)<sup>a</sup> | 4.8 (2.3) | 4.8 (3.1)<sup>b</sup> |
| **t<sub>max</sub>, h, median (min; max)** | 0.9 (0.5; 4.1) | 1.3 (0.5; 12.0) | 0.9 (0.5; 4.1) | 0.8 (0.4; 2.1) |

The number of subjects in the analysis with/without oral semaglutide is lower due to subject withdrawals (2 subjects; 1 of these also affecting the number of subjects in the analysis with/without SNAC)

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Only subjects having evaluable profiles for both treatment periods (e.g. furosemide/rosuvastatin alone and furosemide/rosuvastatin + oral semaglutide or furosemide/rosuvastatin alone + furosemide/rosuvastatin + SNAC alone) were considered for each comparison. The comparisons are presented separately due to the differences in the number of subjects

AUC<sub>0-∞</sub>, area under the plasma concentration–time curve from time zero to infinity, C<sub>max</sub>, maximum concentration, CV, coefficient of variation, max, maximum, min, minimum, SD, standard deviation, SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, t<sub>½</sub>, terminal half-life, t<sub>max</sub>, time to reach maximum concentration

Table 5 Pharmacokinetic endpoints for rosuvastatin (single dose) either alone or after co-administration with oral semaglutide or sodium N-(8-[2-hydroxybenzoyl] amino) caprylate alone

| Parameters | Effect of oral semaglutide | Effect of SNAC |
|------------|----------------------------|----------------|
|            | Rosuvastatin alone (n = 33) | Rosuvastatin + oral semaglutide (n = 33) | Rosuvastatin alone (n = 40) | Rosuvastatin + SNAC alone (n = 40) |
| **AUC<sub>0-∞</sub>, ng·h/mL** | | | | |
| Geometric mean (CV) | 64.1 (45.3) | 90.3 (58.0) | 64.1 (42.9) | 62.0 (39.6) |
| Arithmetic mean (SD) | 70.3 (31.4) | 104.6 (61.1) | 69.7 (29.7) | 66.8 (28.2) |
| **C<sub>max</sub>, ng/mL** | | | | |
| Geometric mean (CV) | 7.5 (63.0) | 8.3 (69.3) | 7.6 (61.5) | 7.0 (58.5) |
| Arithmetic mean (SD) | 8.9 (5.4) | 10.2 (7.8) | 8.9 (5.3) | 8.2 (5.3) |
| **t<sub>½</sub>, h** | | | | |
| Geometric mean (CV) | 17.1 (54.5) | 20.5 (47.7) | 17.0 (51.4) | 16.7 (35.4) |
| Arithmetic mean (SD) | 19.9 (13.9) | 22.6 (10.6) | 19.5 (12.9) | 17.7 (6.4) |
| **t<sub>max</sub>, h, median (min; max)** | 1.0 (0.5; 5.0) | 1.5 (1.0; 10.1) | 1.0 (0.5; 5.0) | 1.0 (1.0; 5.0) |

The number of subjects in the analysis with/without oral semaglutide is lower due to loss of blood samples for pharmacokinetic assessment (6 subjects) and subject withdrawals (2 subjects; 1 of these also affecting the number of subjects in the analysis with/without SNAC)

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Only subjects having evaluable profiles for both treatment periods (e.g. furosemide/rosuvastatin alone and furosemide/rosuvastatin + oral semaglutide or furosemide/rosuvastatin alone + furosemide/rosuvastatin + SNAC alone) were considered for each comparison. The comparisons are presented separately due to the differences in the number of subjects

AUC<sub>0-∞</sub>, area under the plasma concentration–time curve from time zero to infinity, C<sub>max</sub>, maximum concentration, CV, coefficient of variation, max, maximum, min, minimum, SD, standard deviation, SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, t<sub>½</sub>, terminal half-life, t<sub>max</sub>, time to reach maximum concentration
5 Conclusion

When co-administered with oral contraception, neither oral semaglutide nor SNAC alone had a statistically significant effect on the exposure of ethinylestradiol or levonorgestrel. Oral semaglutide resulted in a small increase in exposure to furosemide and rosuvastatin. The clinical relevance of the increased exposure of furosemide and rosuvastatin was not assessed in this trial. However, since furosemide has a broad therapeutic index and is generally dose-adjusted individually, and since rosuvastatin is generally well-tolerated with similar increases in exposures previously being reported as not clinically relevant, the results observed in the present trial are expected to be of no clinical relevance.

Oral semaglutide was found to be well-tolerated in combination with these drugs and no unexpected safety issues were identified.

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Compliance with Ethical Standards

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Conflict of interest Tine A. Bækdal, Erik Christiansen, Azadeh Houshmand-Øregaard, Easwaran Manigandan and Andreas B. Jordy are Novo Nordisk employees. Tine A. Bækdal, Thomas W. Anderson, Erik Christiansen, Azadeh Houshmand-Øregaard and Easwaran Manigandan own stocks or shares in Novo Nordisk. Thomas W. Anderson is a former employee of Novo Nordisk.

Ethical approval All procedures performed in studies involving human subjects were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
Consent to participate  Informed consent was obtained from all individual subjects included in these trials.

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