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ORIGINAL RESEARCH

A randomized study investigating the effect of omeprazole on the pharmacokinetics of oral semaglutide

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ABSTRACT

Background: Since the first oral glucagon-like peptide-1 analog comprises semaglutide co-formulated with an absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, which induces a transient, localized increase in gastric pH, we have investigated whether a proton pump inhibitor affects the pharmacokinetics of oral semaglutide.

Research design and methods: A single-center, randomized, open-label, parallel-group trial investigated pharmacokinetic interactions of oral semaglutide with omeprazole (40 mg once-daily) in 54 healthy subjects. Primary endpoints were area under the plasma concentration-time curve over 24 h for semaglutide ($AUC_{0-24h,semaglutide,Day10}$) and maximum concentration of semaglutide ($C_{max,semaglutide,Day10}$) at day 10.
Results: Exposure of semaglutide appeared to be slightly increased, although not statistically significantly, with oral semaglutide plus omeprazole versus oral semaglutide alone ($AUC_{0-24h,semaglutide,Day10}$ [estimated treatment ratio 1.13; 90%CI 0.88, 1.45] and $C_{max,semaglutide,Day10}$ [estimated treatment ratio 1.16; 90%CI 0.90, 1.49]). Gastric pH was higher with oral semaglutide and omeprazole versus oral semaglutide alone. Adverse events were mild or moderate and, most commonly, gastrointestinal disorders.
Conclusions: There was a slight non-statistically significant increase in semaglutide exposure when oral semaglutide was administered with omeprazole, but this is not considered clinically relevant and no dose adjustment is likely to be required.

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GLP-1 receptor agonists; semaglutide; pharmacokinetics; omeprazole; drug interactions

1. Introduction

The glucagon-like peptide-1 (GLP-1) receptor represents a valuable target for the management of type 2 diabetes, based on its abilities to stimulate insulin, inhibit glucagon secretion in a glucose-depending manner, delay gastric emptying, and reduce energy intake with a low risk of hypoglycemia [1,2], and the potential for cardiovascular protection [3,4]. Several GLP-1 receptor agonists (GLP-1RAs) are available (liraglutide, lixisenatide, albiglutide, dulaglutide, and exenatide) and are administered by subcutaneous injection on a daily or weekly basis. However, oral administration of GLP-1-based therapies will provide an alternative route of delivery and greater convenience for some patients with type 2 diabetes, and thereby may help with patient acceptance and adherence.

The first orally delivered GLP-1 analog in clinical development for the treatment of type 2 diabetes is based on semaglutide, a GLP-1 analog shown to be effective at improving glycemic control, reducing body weight, and potentially providing cardiovascular protection in patients with type 2 diabetes when administered subcutaneously [3,5,6]. Oral semaglutide comprises a co-formulation of semaglutide with the absorption enhancer, sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC), in a tablet [7]. The mode of action of SNAC involves a buffering effect that increases the local pH, protecting semaglutide against proteolytic degradation and facilitating the highly localized absorption of semaglutide across gastric mucosa in a concentration-dependent manner via effects on transcellular pathways [8,9]. In a phase 2 dosage-finding trial in 632 patients with type 2 diabetes, once-daily oral semaglutide resulted in better glycemic control and greater weight loss than placebo over 26 weeks [7].

As the enhanced absorption of semaglutide is facilitated by SNAC in a pH-dependent manner, it is important to determine if treatments that change gastric pH influence the effects of SNAC and thereby alter the exposure to semaglutide. Proton pump inhibitors (PPIs) are a commonly used approach to alleviate symptoms of various gastrointestinal comorbidities in patients with type 2 diabetes. These agents act by inhibiting the acid pump in parietal cells of the stomach to increase gastric pH [10], with the largest decreases in acid secretion occurring around 2 h after administration [11,12]. The inhibitory effect on acid secretion increases with repeated once-daily dosing, reaching a plateau after 4 days [12].

The current trial was conducted in order to investigate whether administration of the commonly prescribed PPI, omeprazole, affects the pharmacokinetics (PK) of oral semaglutide.

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This article has been republished with minor changes. These changes do not impact the academic content of the article.

Trial registration: The trial is registered at clinicaltrials.gov (identifier: NCT02249871).

Supplemental data for this article can be accessed here.

2. Patients and methods

An independent ethics committee, Landesamt für Gesundheit und Soziales, Berlin, approved the protocol. All subjects provided written, informed consent. The trial was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and US Food and Drug Administration (FDA)/European Medicines Agency (EMA) guidelines for drug-drug interaction studies [13,14].

2.1. Trial population

Healthy male and female subjects aged 18 to 75 years and with a body mass index of 20.0 to 29.9 kg/m^2 were eligible to participate if they were in good general health, based on medical history, physical examination, and assessment of vital signs, electrocardiogram, and laboratory safety tests. Key exclusion criteria included a history, or presence, of cancer, diabetes, or any clinically significant cardiovascular, respiratory, metabolic, renal, hepatic, gastrointestinal, endocrinological, hematological, dermatological, venereal, neurological, psychiatric diseases, or other major disorder; previous gastrointestinal surgery; history of Crohn's disease, ulcerative colitis, or other inflammatory bowel disease (full eligibility criteria are listed in Supplementary Online Material). Prescription or non-prescription medicinal or herbal products were not allowed within 3 weeks before or during the trial, other than the use of contraceptives, occasional use of paracetamol (up to 3000 mg daily [3 × 1000 mg]), and use of local anesthetics for gastric pH measurement procedures.

2.2. Trial design

This was a randomized, open-label, parallel-group trial (NCT02249871) conducted at a single site (Early Phase Clinical Unit, PAREXEL International GmbH, Berlin, Germany) between September 2014 and April 2015. Subjects were stratified by sex and randomized (1:1) to oral semaglutide once-daily (5 mg for 5 days, followed by 10 mg for 5 days), either with or without concomitant administration of omeprazole 40 mg gastro-resistant capsules once-daily (Figure 1) using randomization lists. The 10-day dosing regimen was chosen to avoid subjects with semaglutide exposure below the lower limit of quantification (LLOQ) and reduce the variability observed in exposure after a single dose [15]. In addition, the multiple dose regimen ensured a maximal effect on acid secretion.

After oral administration of omeprazole, the onset of the anti-secretory effect occurs within 1 h, with the maximum effect from 2 h after dosing [12]. To investigate the exposure of semaglutide and SNAC at the time of the expected maximum effect of omeprazole on gastric pH, oral semaglutide was dosed 2 h after intake of omeprazole in the current trial. Both trial products were administered with 120 mL of water. In subjects not receiving omeprazole, 120 mL of water was given alone 2 h before semaglutide administration. Subjects did not consume food or liquid other than water 6 h prior to dosing of semaglutide. No water intake was permitted in the 2 h before dosing of semaglutide. Subjects were not permitted food or liquid intake for 30 min after dosing of oral semaglutide, after which a meal was served.

Blood samples were drawn into K_3EDTA tubes pre-dose on day 1, and at set time points on days 9 and 10, for determination of plasma semaglutide and SNAC concentrations (see Supplementary Online Material for exact timings), and stored at – 20°C until analyzed.

To determine plasma semaglutide concentrations, a liquid chromatography tandem-mass spectroscopy (LC-MS/MS) assay was used following precipitation of the plasma proteins (validated according to current guidelines for bioanalysis of plasma samples in the concentration range 0.729 to 60.8 nmol/L [3.00 to 250 ng/mL], including extension of the assay range 5-fold by dilution) (Celerion Switzerland AG, Fehraltorf, Switzerland). A stable isotope-labeled analog of semaglutide was used as an internal standard. The analysis was conducted using an *AB* SCIEX API QTRAP® 5500 mass spectrometer and positive ions were monitored in the multiple reaction-monitoring mode with mass transitions m/z 1029.1→136.0 Da (semaglutide) and m/z 1033.2→136.0 Da (internal standard). The liquid chromatography (LC) system was a Waters ACQUITY UPLC System and the LC column an ACQUITY UPLC BEH300 C18, 2.1 × 50 mm. Quantification was performed by peak area ratios of semaglutide compared to the internal standard. The calibration curve was fitted by a

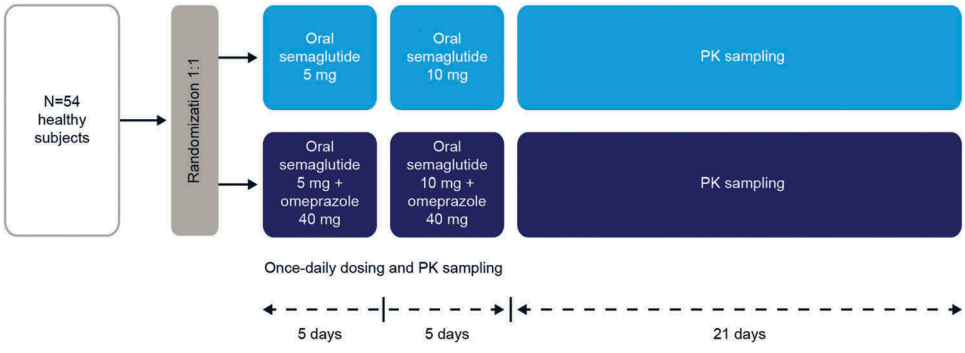

Figure 1. Trial design.
PK, pharmacokinetics.

weighted linear regression (1/concentration^2). The LLOQ for semaglutide was 0.729 nmol/L (see Supplementary Online Material for rules on imputation of values below the LLOQ).

For the bioanalysis of SNAC, an LC-MS/MS assay was used following in-line solid-phase sample preparation (validated according to current guidelines for bioanalysis of plasma samples in the concentration range 5.00 to 2000 ng/mL, including extension of the assay range 5-fold by dilution) (Celerion Switzerland AG, Fehraltorf, Switzerland). A structural analog of SNAC was used as an internal standard. The analysis was conducted using an *AB* SCIEX API 4000™ Triple Quadrupole Mass Spectrometer and negative ions monitored in the MRM mode with mass transitions m/z 278.1→118.0 Da (SNAC) and m/z 249.0→135.0 Da (internal standard). The LC system was a Cohesive Turbulent Flow system with LC loading column, Turboflow Cyclone-P, 50 × 0.5 mm, and analytical column Onyx™ Monolithic C18, 50 × 2.0 mm. Quantification was performed using the peak area ratios of SNAC compared to the internal standard. The calibration curve was fitted by a weighted linear regression (1/concentration^2). The LLOQ for SNAC was 5.00 ng/mL (see Supplementary Online Material for rules on imputation of values below the LLOQ).

Omeprazole is completely metabolized by the cytochrome P450 system (CYP), particularly CYP2C19, and CYP2C19 is also inhibited by omeprazole [16]. CYP2C19 genotyping was conducted on blood samples, using validated sequencing assays and the ABI 3130 Genetic Analyzer or PGM Ion Torrent™ (Life Technologies).

Gastric pH measurements were performed on day −1 and day 9 (to prevent the pH measurement procedure from influencing semaglutide absorption and exposure on day 10 [primary endpoint timepoint]). A pH catheter was inserted into the stomach via a nostril and the ZepHr® Impedance/pH Reflux Monitoring System was used. The pH measurements were started at the time of omeprazole dosing (day 9, oral semaglutide plus omeprazole group) or at least 5 min before intake of 120 mL water in patients not receiving omeprazole (day – 1 and day 9; oral semaglutide group), and pH measurements were recorded every 5 s for 5 h.

2.3. Sample size and statistical methods

The sample size was based on the precision of the ratio for the primary endpoint, area under the plasma concentration-time curve (AUC) for semaglutide from time 0 to 24 h after the 10th dosing ($AUC_{0-24h,semaglutide,Day10}$), between the two treatment groups using a two-sided 95% confidence interval (CI) derived from the *t*-distribution. With 24 evaluable profiles at end of treatment in each of the groups, assuming a standard deviation for log ($AUC_{0-24h,semaglutide,Day10}$) of 0.6 and no difference between males and females, there was at least 80% probability to get a 95%CI for the ratio R of $AUC_{0-24h,semaglutide,Day10}$ between the two treatment groups within (0.68*R; 1.46*R). Assuming a withdrawal rate of 10%, 54 subjects were planned for randomization (27 per group).

The primary endpoint, $AUC_{0-24h,semaglutide,Day10}$, was log-transformed and analyzed (SAS version 9.3) using an analysis of variance model with treatment group (two levels) and sex as fixed factors. This analysis was based on the full analysis set, which was defined as subjects who were randomized and exposed. The mean difference in log-transformed $AUC_{0-24h,semaglutide,Day10}$ between the two groups was estimated and back-transformed to the original scale and presented as a ratio together with the corresponding two-sided 90%CI.

The secondary endpoint of maximum observed plasma concentration for semaglutide after the 10th dosing ($C_{max,semaglutide,Day10}$) was analyzed similarly. Time to maximum semaglutide concentration ($t_{max,semaglutide,Day10}$) and half-life of oral semaglutide ($t_{½,semaglutide,Day10}$) were summarized using descriptive statistics.

Relationships between three gastric pH parameters and the PK of semaglutide and SNAC were also explored. The area under the pH measurements-time curve from 0 to 3 h after the 9th daily dose of oral semaglutide divided by the actual time interval during which pH measurements were being taken ($AUC_{0-3h,pH,Day9}$/time) was calculated using the linear trapezoidal method. The maximum observed pH measurement 0 to 3 h after the 9th oral semaglutide dose ($pH_{max,Day9}$) was derived as the maximum of all valid pH measurements within the time frame. The incremental area under the pH measurement-time curve from 0 to 3 h after the 9th oral semaglutide dose divided by the actual time interval during which pH measurements were being taken ($iAUC_{0-3h,pH,Day9}$/time) was calculated using the linear trapezoidal method as the area under the pH measurement-time curve that is above the pre-dose pH average, taken as the average of pH values 5 min up to dosing at nominal time – 2 h in relation to the 9th dose.

Safety was evaluated in all subjects who were exposed to at least one dose of trial product (safety analysis set). Safety was assessed by the number of treatment-emergent adverse events (TEAEs), number of hypoglycemic episodes, changes in laboratory safety variables, physical examination, vital signs, and electrocardiogram.

3. Results

In total, 114 subjects were screened, and 54 subjects were randomized and exposed to trial products (Figure 2). Of these subjects, 53 completed the trial; one subject withdrew due to a TEAE (acute tonsillitis). All 54 subjects were included in the full analysis and safety analysis set.

Demographic and baseline characteristics are shown in Table 1. The mean age of the subjects was 52 years in the oral semaglutide group and 59 years in the oral semaglutide plus omeprazole group. There were no apparent differences in other baseline characteristics between treatment groups. Two subjects in the oral semaglutide plus omeprazole group were poor metabolizers with regards to CYP2C19 phenotyping, while all other subjects were extensive metabolizers.

3.1. Semaglutide pharmacokinetics

The geometric mean concentration-time profiles of semaglutide for one dosing interval (24 h) after the 10th dose are shown in Figure 3(a). Exposure to semaglutide after the 10th dose ($AUC_{0-24h,semaglutide,Day10}$) appeared to be slightly higher

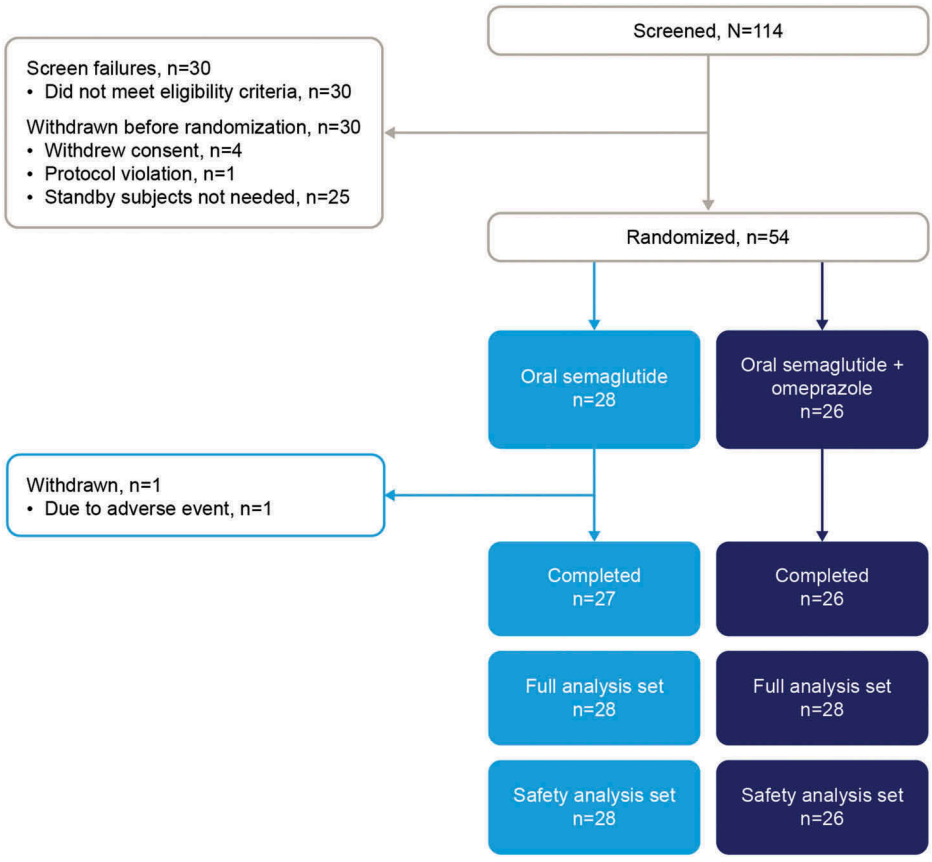

Figure 2. Subject flow.

in the oral semaglutide plus omeprazole group compared with oral semaglutide alone; however, the increase was not statistically significant (estimated treatment ratio 1.13; 90%CI 0.88, 1.45) (Figure 3(b)). Similarly, $C_{max,semaglutide,Day10}$ appeared to be slightly higher with oral semaglutide plus omeprazole compared with oral semaglutide alone, but the difference was not statistically significant (Figure 3(b)). Median $t_{max,semaglutide,Day10}$ was the same in subjects receiving oral semaglutide plus omeprazole and in those receiving oral semaglutide alone (1.0 h for both groups) (Table 2). In addition, $t_{½}$ for semaglutide was similar in subjects treated with oral semaglutide plus omeprazole (geometric mean of 156 h) and those treated with oral semaglutide alone (150 h) (Table 2).

Results for semaglutide PK parameters after the 9th dosing (Supplemental Table S1) at the time of gastric pH measurement were consistent with results obtained after the 10th dosing, the time of primary PK endpoint assessment.

Table 1. Baseline demographic and clinical characteristics.

	Oral semaglutide (*N* = 28)	Oral semaglutide + omeprazole (*N* = 26)
Sex, *n* (%)		
Male	12 (42.9)	11 (42.3)
Female	16 (57.1)	15 (57.7)
Age, years		
Mean (*SD*)	52 (13)	59 (7)
Median (min, max)	55 (26, 74)	60 (44, 72)
CYP2C19 metabolizer phenotype, n (%)		
Extensive	28 (100.0)	24 (92.3)
Intermediate	0	0
Poor	0	2 (7.7)
Body weight, kg		
Mean (*SD*)	75.1 (12.6)	74.3 (13.0)
Median (min, max)	75.2 (47.6, 97.4)	73.8 (54.7, 104.2)
Height, m		
Mean (*SD*)	1.73 (0.10)	1.73 (0.10)
Median (min, max)	1.75 (1.53, 1.92)	1.72 (1.55, 1.93)
Body mass index, kg/m^2		
Mean (*SD*)	24.9 (2.8)	24.8 (2.3)
Median (min; max)	24.4 (20.3, 29.9)	24.4 (21.6, 29.4)

%, percentage of subjects; CYP, cytochrome P450 system; SD, standard deviation.

3.2. SNAC pharmacokinetics

As shown in Figure 4(a), the pattern of exposure to SNAC was similar in the oral semaglutide plus omeprazole group compared with oral semaglutide alone after the 10th dosing (Figure 4(a)). The $AUC_{0–24h,SNAC,Day10}$ of SNAC appeared to be slightly higher in the oral semaglutide plus omeprazole group compared with oral semaglutide alone (estimated treatment ratio 1.14; 90%CI 1.02, 1.27) (Figure 4(b)). The maximum exposure of SNAC ($C_{max,SNAC,Day10}$) was similar and not significantly different between the two groups (estimated treatment ratio 0.96; 90%CI 0.72, 1.29) (Figure 4(b)).

The median $t_{max,SNAC,Day10}$ for SNAC after the 10th daily dose was similar between the groups (0.7 h with oral semaglutide and 0.6 h with oral semaglutide plus omeprazole)

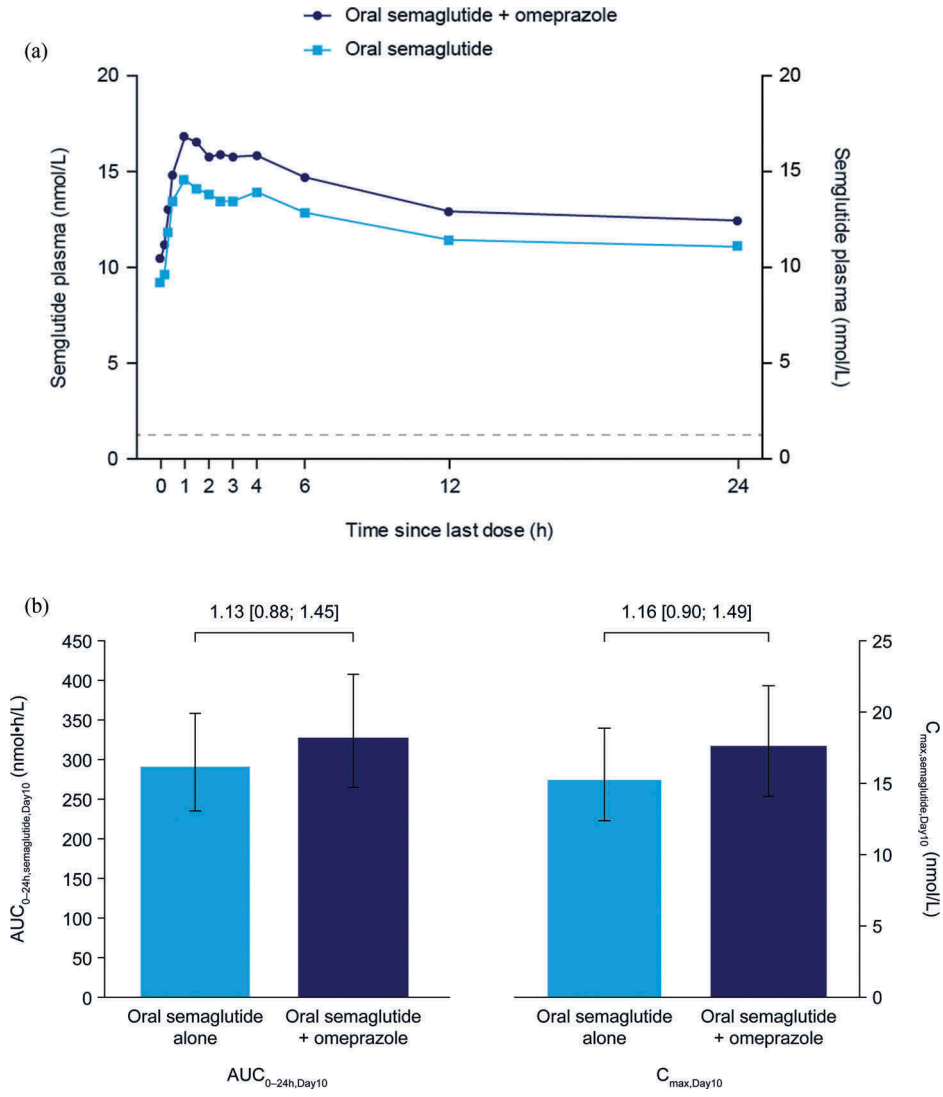

Figure 3. Pharmacokinetics of semaglutide after the 10th dosing (a) Geometric mean plasma concentration-time profile of semaglutide. Dotted line indicates LLOQ. Values below LLOQ were imputed (see Supplementary Online Material). (b) Comparison of AUC_{0-24h} and C_{max} for semaglutide between the oral semaglutide and oral semaglutide plus omeprazole groups. Bars are estimated means and 95% confidence intervals. Treatment comparisons show estimated treatment ratio (oral semaglutide + omeprazole/oral semaglutide) and 90% confidence interval.

AUC, area under the plasma concentration-time curve; C_{max}, maximum semaglutide concentration; LLOQ, lower limit of quantification.

(Table 2). No clear terminal phase was observed for SNAC; hence, $t_{½}$ could not be estimated. However, the mean concentration of SNAC in plasma had declined to less than LLOQ in most patients within 24 h, indicating fast elimination.

Results for SNAC PK parameters after the 9th dosing (Supplemental Table S1) were consistent with results obtained after the 10th dosing.

3.3. Effects on gastric pH parameters

Overall, an increase in gastric pH was observed on day 9 in subjects in the oral semaglutide plus omeprazole group compared to the oral semaglutide alone group. The means of $AUC_{0-3h,pH,Day9}$/time, $iAUC_{0-3h,pH,Day9}$/time, and $pH_{max,Day9}$ appeared higher in the oral semaglutide plus omeprazole group compared with the oral semaglutide alone group (Table 3).

Scatter plots presenting the association of semaglutide exposure ($AUC_{0-24h,Day9}$) and the gastric pH parameters did not indicate any pattern or relationship (linear or non-linear) between treatments (Supplemental Figure S1). The two CYP2C19 poor metabolizers were distributed across the plot similarly to the extensive metabolizers, without displaying any specific pattern. In exploratory analyses, there were no statistically significant associations between AUC_{0-24h} or C_{max} (day 9 and 10) for semaglutide and the gastric pH parameters measured (Supplemental Table S2). Scatter plots presenting the association of SNAC exposure ($AUC_{0-24h,Day9}$) and the gastric pH parameters did not appear to show a specific pattern (Supplemental Figure S2). In exploratory analyses, the estimates of coefficients were positive and there was a significant association between C_{max} of

Table 2. Pharmacokinetic endpoints for semaglutide and SNAC after the 10th dosing.

	Oral semaglutide (N = 28)	Oral semaglutide + omeprazole (N = 26)
Semaglutide		
$AUC_{0-24h,semaglutide,Day10}$, estimated means (95%CI), nmol·h/L	290 (235, 358)	328 (265, 407)
$C_{max,semaglutide,Day10}$, estimated means (95%CI), nmol/L	15.2 (12.3, 18.8)	17.6 (14.1, 21.8)
$t_{max,semaglutide,Day10}$, median (min, max), h	1.0 (0.2, 4.0)	1.0 (1.0, 6.0)
$t_{½}$, geometric mean (CV), h	150 (9.6)	156 (9.5)
SNAC		
$AUC_{0-24h,SNAC,Day10}$, estimated means (95%CI), ng·h/mL	1129 (1029, 1238)	1284 (1169, 1410)
$C_{max,SNAC,Day10}$, estimated means (95%CI), ng/mL	1028 (804, 1314)	986 (768, 1267)
$t_{max,SNAC,Day10}$, median (min, max), h	0.7 (0.2, 4.0)	0.6 (0.1, 10.0)
$t_{½}$, geometric mean (CV), h	–	–

AUC, area under the plasma concentration–time curve; CI, confidence intervals; CV, coefficient of variation; h, hour; SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate; t_{max}, time to maximum; $t_{1/2}$, half life.

SNAC and $pH_{max,0-3h}$ on day 9; however, no statistical association was found between C_{max} of SNAC on day 10 and $pH_{max,0-3h}$ on day 9. There were no other statistically significant associations between AUC_{0-24h} or C_{max} (day 9 and 10) for SNAC and the gastric pH parameters measured (Supplemental Table S3).

3.4. Safety and tolerability

A total of 74 TEAEs were reported by 27 subjects (50%) across the two treatment groups (39 events in 17 subjects in the oral semaglutide group and 35 events in 10 subjects in the oral semaglutide plus omeprazole group). All of the TEAEs were mild (62 events) or moderate (12 events) in severity and all were reported as recovered. The most frequently reported TEAEs were gastrointestinal disorders (29 events in 17 subjects), including nausea and abdominal distension, followed by metabolism and nutrition disorders (12 events in 12 subjects), particularly decreased appetite (Supplemental Table S4). One subject treated with oral semaglutide alone withdrew due to a non-serious TEAE (acute tonsillitis). No serious TEAEs or deaths were reported. No medical events of special interest (pancreatic neoplasms, pancreatitis or clinical suspicion of pancreatitis, or medication errors concerning trial products) were reported.

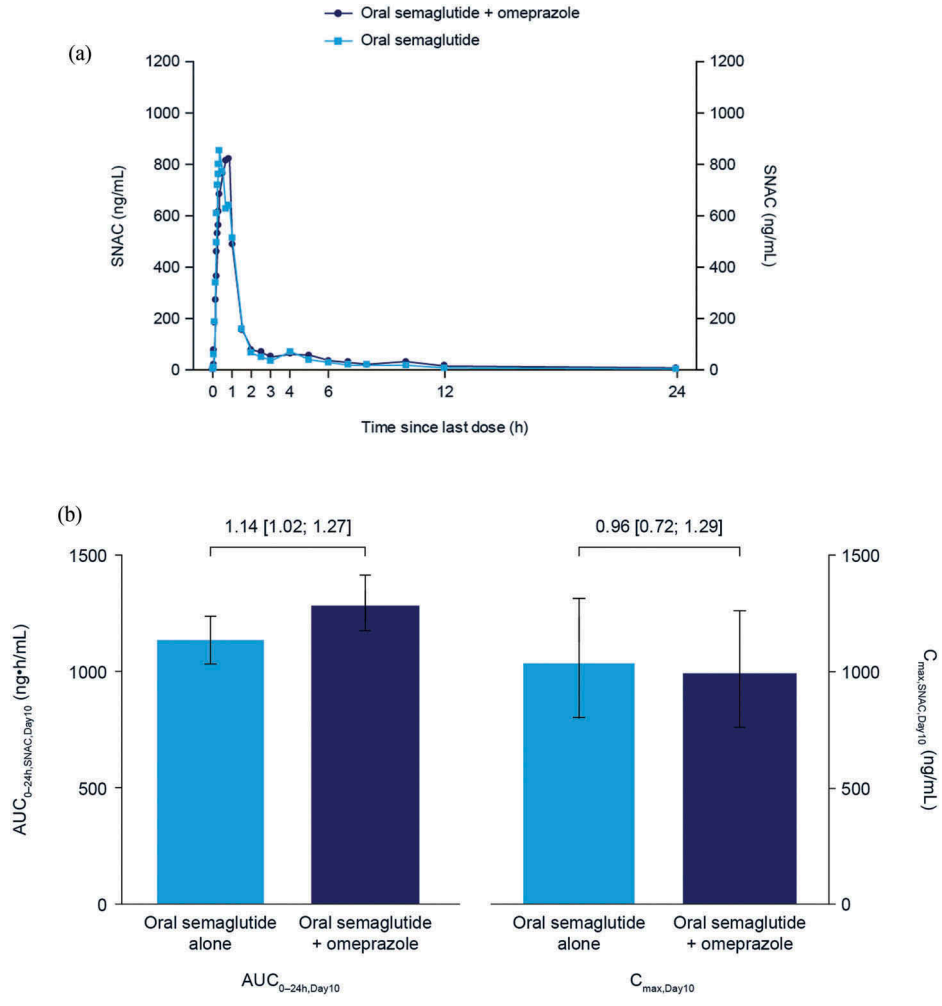

Figure 4. Pharmacokinetics of SNAC after the 10th dosing. (a). Mean plasma concentration–time profile of SNAC. (b) Comparison of AUC_{0-24h} and C_{max} for SNAC between the oral semaglutide and oral semaglutide plus omeprazole groups. Bars are estimated means and 95% confidence intervals. Treatment comparisons show estimated treatment ratio (oral semaglutide + omeprazole/oral semaglutide) and 90% confidence interval.

AUC, area under the plasma concentration-time curve; C_{max}, maximum SNAC concentration; SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.

Table 3. Gastric pH parameters after the 9th dosing.

	Oral semaglutide (*N* = 28)	Oral semaglutide + omeprazole (*N* = 26)
$AUC_{0-3h,pH,Day9}$/time		
n	27	26
Mean (*SD*)	2.5 (1.42)	4.8 (1.78)
Geometric mean (*CV*)	2.3 (45.0)	4.4 (51.4)
Median (min, max)	2.0 (1.2, 6.8)	4.9 (1.2, 8.5)
$pH_{max,Day9}$		
n	27	26
Mean (*SD*)	6.0 (1.58)	7.1 (1.34)
Geometric mean (*CV*)	5.7 (33.0)	7.0 (19.8)
Median (min, max)	6.1 (1.8, 9.0)	7.2 (4.6, 9.6)
$iAUC_{0-3h,pH,Day9}$/time		
n	27	26
Mean (*SD*)	0.6 (0.58)	1.6 (1.65)
Geometric mean (*CV*)	0.3 (287.7)	0.6 (670.1)
Median (min, max)	0.4 (0.0, 2.0)	1.0 (0.0, 5.7)

AUC, area under the plasma concentration–time curve; CV, coefficient of variation in %; n, number of subjects in the descriptive statistics; SD, standard deviation.

No hypoglycemic episodes were reported during the trial. No clinically relevant changes in vital signs, laboratory parameters, physical examination, or electrocardiogram were observed. Pulse rate increased comparably in both treatment groups and changes were not considered clinically relevant at an individual level.

4. Discussion

To facilitate absorption upon oral administration, semaglutide has been co-formulated with SNAC, which induces a localized, transient increase in gastric pH, protecting semaglutide from proteolytic degradation and enhancing absorption [8,9]. Few drug-drug interaction studies have previously been published with omeprazole and other GLP-1RAs due to their subcutaneous administration. However, due to the mechanism of action of SNAC in oral semaglutide, the present trial was conducted to investigate the potential influence of omeprazole-mediated gastric pH increase on the systemic exposure of semaglutide and SNAC.

As expected, gastric pH increased with omeprazole administration. Omeprazole administration appeared to have no substantial impact on the exposure of SNAC. The $AUC_{0-24h,Day10}$ of SNAC was 14% higher in the oral semaglutide plus omeprazole group compared with semaglutide alone, although C_{max} and t_{max} for SNAC were similar between the groups. Omeprazole treatment was associated with a slight but not statistically significant increase in exposure to semaglutide ($AUC_{0-24h,Day10}$ and $C_{max,Day10}$) versus oral semaglutide taken alone. Furthermore, median t_{max} and $t_{½}$ appeared similar in subjects treated with oral semaglutide plus omeprazole and those treated with oral semaglutide alone. The slight, apparent increase in exposure to semaglutide with omeprazole was not considered to be clinically relevant, as semaglutide has a broad therapeutic index and the change was well within the margins defined by the FDA and EMA for moderate inhibition [13,14]. Data from the phase 2 study, where oral semaglutide from 2.5 mg to 40 mg once-daily was studied, indicate that oral semaglutide is clinically effective and well tolerated in a broad range of doses and exposures [7] and, as such, slight increases in exposure are unlikely to affect the clinical outcomes or safety profile of oral semaglutide in patients treated with a PPI.

Gastric pH reaches its lowest levels during fasting (pH 1–2) and highest after food intake (up to pH 4), with omeprazole increasing both the fasting and fed gastric pH levels [17,18]. To maximize the inhibition of proton pumps on gastric parietal cells, and thus the inhibitory effects on acid secretion, PPIs are typically taken 20–30 min before meals. However, while this dosing might result in a maximal clinical anti-secretory effect, the purpose of this trial was to test the effect of an increased pH. Thus, in the present trial, omeprazole was dosed 2 h before oral semaglutide so that the time of oral semaglutide tablet disintegration coincided with the expected peak anti-secretory effect of omeprazole. Although this regimen might not be representative of omeprazole and oral semaglutide dosing in clinical practice, which is a potential limitation of our trial, the dosing schedule was selected to reflect a worst-case scenario that produced the potential maximum effect of omeprazole on the PK of oral semaglutide. We also selected a relatively high dose of omeprazole 40 mg/day, which is indicated for the treatment of gastric ulcers [12]. Thus, administration of omeprazole to a different schedule or dose with oral semaglutide in real life is unlikely to influence semaglutide exposure to a greater degree than that reported here.

In the present trial, omeprazole was administered with 120 mL of water. Although the potential effect of this water consumption on semaglutide exposure was not compared with a complete fasting state, a previous study had indicated that semaglutide exposure was not significantly affected by water volume [19].

Omeprazole inhibits its own CYP2C19-mediated metabolism and poor metabolizers of CYP2C19 have been shown to have higher gastric pH after treatment with omeprazole compared to extensive metabolizers [20]. In the present trial, there appeared to be no association between gastric pH, exposure to semaglutide, and CYP2C19 metabolizer status.

Limitations of the current trial include that any direct effects of omeprazole on the pharmacodynamics of oral semaglutide were not elucidated. Another possible limitation is the open-label design; however, the design is in line with FDA and EMA guidelines on drug-drug interaction studies [13,14]. The open-label design is unlikely to have affected interpretation of PK endpoints, especially with all doses being administered on site, although this could have influenced the reporting of adverse events. Nevertheless, the safety profile of oral semaglutide was consistent with trials assessing oral and subcutaneous semaglutide in patients with type 2 diabetes [5–7,21–24] and did not appear to be affected by omeprazole co-administration. The most frequently reported TEAEs with semaglutide were gastrointestinal disorders, which are considered a class effect of GLP-1RAs. No serious TEAEs, deaths, or hypoglycemic episodes were reported.

5. Conclusions

In conclusion, there was a slight non-statistically significant increase in semaglutide exposure when oral semaglutide was administered with omeprazole at the time of maximum anti-secretory effect. This is considered non-clinically relevant and,

as such, no dose adjustment of oral semaglutide is likely to be required when administered with omeprazole.

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Declaration of interest

TA Bækdal is an employee of Novo Nordisk A/S and own stocks in the company; A Breitschaft is an employee of PAREXEL International GmbH; C W Hansen and A Navarria are employees of Novo Nordisk A/S. All trial subjects received remuneration from Novo Nordisk A/S for trial participation and this was approved by the Ethics Committee. Writing assistance and editorial support, provided by Graham Allcock of Spirit Medical Communications Ltd., was utilized in the writing of this paper and funded by Novo Nordisk A/S. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer declaration of interest

A reviewer on this manuscript has disclosed that they are an investigator on the oral semaglutide clinical trials.

Author Contribution Statement

All authors participated in the conception and trial design. *AB* was involved in the trial conduct and acquisition of data. All authors were involved in data analysis and interpretation, and participated in drafting of the manuscript or revising it critically for intellectual content. All authors have approved the submitted manuscript and agree to be accountable to all aspects of the work.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696–1705.
2. Verspohl EJ. Novel therapeutics for type 2 diabetes: incretin hormone mimetics (glucagon-like peptide-1 receptor agonists) and dipeptidyl peptidase-4 inhibitors. Pharmacol Ther. 2009;124:113–138.
3. Marso SP, Bain SC, Consoli A, et al. SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–1844.
4. Marso SP, Daniels GH, Brown-Frandsen K, et al. LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–322.
5. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5:341–354.
6. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5:251–260.
7. Davies M, Pieber TR, Artoft-Nielsen ML, et al. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: A randomized clinical trial. JAMA. 2017;318(15):1460–1470.
•• **This phase 2 randomized clinical trial is the first clinical study to confirm that oral semaglutide resulted in improved glycemic control and reduced body weight compared with placebo.**
8. Buckley ST, Schéele SG, Kirk RK, et al. Mechanism of absorption mediated by SNAC in an oral formulation of semaglutide. Diabetes. 2017;66(Suppl 1):1206–P.
• ***In vitro* data demonstrate that SNAC promotes absorption of semaglutide across gastric mucosa in a concentration-dependent manner via effects on transcellular pathways and that the absorption-enhancing effect of SNAC is both transient and fully reversible.**
9. Connor A, Borregaard J, Buckley ST, et al. Site of absorption of an oral formulation of semaglutide. Diabetes. 2017;66(Suppl 1):1180–P.
• **Clinical and non-clinical data suggest that orally administered semaglutide is absorbed in a highly localized manner in the stomach.**
10. Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD: an overview of their pharmacology, efficacy and safety. Pharmacol Res. 2009;59(3):135–153.
11. Gan KH, Geus WP, Lamers CB, et al. Effect of omeprazole 40 mg once daily on intraduodenal and intragastric pH in H. pylori-negative healthy subjects. Dig Dis Sci. 1997;42(11):2304–2309.
12. Food and Drug Administration. Prilosec prescribing information. 2012 [cited 2017 Oct 28]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019810s096lbl.pdf.
13. Food and Drug Administration. Drug interaction studies – study design, data analysis, implications for dosing and labeling recommendations. 2017 Oct. [cited 2017 Oct 20]. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf.
14. European Medicines Agency. Guideline on the investigation of drug interactions. 2012 June 21 [cited 2017 Oct 20]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf.
15. Bækdal TA, Blicher TM, Donsmark M, et al. Safety, tolerability, and pharmacokinetics of single escalating doses of oral semaglutide in healthy male subjects. Diabetes. 2017;66(Suppl.1):1191–P.
16. Shirasaka Y, Sager JE, Lutz JD, et al. Inhibition of CYP2C19 and CYP3A4 by omeprazole metabolites and their contribution to drug-drug interactions. Drug Metab Dispos. 2013;41:1414–1424.
17. Viani F, Verdú EF, Idström JP, et al. Effect of omeprazole on regional and temporal variations in intragastric acidity. Digestion. 2002;65(1):2–10.
18. Prichard PJ, Yeomans ND, Mihaly GW, et al. Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology. 1985;88(1 Pt 1):64–69.
19. Bækdal TA, Borregaard J, Donsmark M, et al. Evaluation of the effects of water volume with dosing and post-dose fasting period on pharmacokinetics of oral semaglutide. Diabetes. 2017;66(Suppl 1):1179–P.
20. Hagymási K, Müllner K, Herszényi L, et al. Update on the pharmacogenomics of proton pump inhibitors. Pharmacogenomics. 2011;12(6):873–888.
21. Granhall C, Donsmark M, Golor G, et al. Safety, tolerability, and pharmacokinetics of multiple dosing of oral semaglutide in healthy males and males with T2D [abstract 1192]. Presentation at 77th American Diabetes Association Meeting; 2017 June 9–13; San Diego, CA .

22. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017;5:355–366.
23. Kapitza C, Dahl K, Jacobsen JB, et al. Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial. Diabetologia. 2017;60:1390–1399.
24. Nauck MA, Petrie JR, Sesti G, et al. Study 1821 Investigators. A Phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with Type 2 diabetes. Diabetes Care. 2016;39(2):231–241.