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ORIGINAL ARTICLE

Effect of upper gastrointestinal disease on the pharmacokinetics of oral semaglutide in subjects with type 2 diabetes

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Abstract

Aim: To investigate whether upper gastrointestinal (GI) disease has any effect on the exposure of oral semaglutide, an important consideration given that its absorption occurs primarily in the stomach.

Materials and Methods: In an open-label, parallel-group trial (NCT02877355), subjects aged 18-80 years with type 2 diabetes with mild-to-moderate upper GI disease (N = 36; chronic gastritis [n = 5], gastroesophageal reflux disease [n = 8], and both [n = 23]) or without upper GI disease (N = 19) received oral semaglutide 3 mg once daily for 5 days, followed by 7 mg for 5 days. The primary and key supportive endpoints were the area under the semaglutide plasma concentration–time curve (AUC) from 0 to 24 hours after last trial product administration on day 10 ($AUC_{0-24h,day10}$) and the maximum semaglutide plasma concentration ($C_{max,day10}$), respectively.

Results: Semaglutide exposure was not statistically significantly different between subjects with and without upper GI disease. Estimated group ratios (subjects with/without upper GI disease) were 1.18 (95% confidence interval [CI], 0.80, 1.75) for $AUC_{0-24h,day10}$ and 1.16 (95% CI, 0.77, 1.76) for C_{max}. Time to C_{max} and semaglutide half-life were similar in subjects with and without upper GI disease. Oral semaglutide was well tolerated; all adverse events were mild-to-moderate, with no withdrawals because of adverse events.

Conclusions: There was no significant difference in exposure to oral semaglutide in subjects with or without upper GI disease, hence no dose adjustment is required.

KEYWORDS
GLP-1RA, pharmacokinetics, type 2 diabetes

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective therapies for the treatment of type 2 diabetes (T2D)[1,2] and, until recently, were only available as formulations administered by subcutaneous injection. Persistence with injectable glucose-lowering agents is low[3] and an oral GLP-1RA provides an alternative route for delivery,[4] which may be preferred by some patients compared with injectable formulations.[5] However, peptide-based drugs, such as GLP-1RAs, have a very low bioavailability when administered orally because of poor absorption across the gastrointestinal (GI) barrier and degradation by proteolytic enzymes within the GI tract.

The first orally delivered GLP-1RA, oral semaglutide, has been shown to improve glycaemic control and reduce body weight in patients with T2D.[6-13] To enable oral delivery, semaglutide has been co-formulated with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). The mode of action of SNAC involves (i) a buffering effect that increases the local pH to protect semaglutide against proteolytic degradation; (ii) indirect prevention of semaglutide self-association; and (iii) the facilitation of a highly localized absorption of semaglutide across gastric mucosa in a concentration-dependent manner via effects on transcellular pathways.[14]

In vivo and *in vitro* studies indicate that the main site of absorption of oral semaglutide is the stomach.[14] Upper GI tract co-morbidities, such as chronic gastritis and gastroesophageal reflux disease (GERD), are common in patients with T2D,[15-17] and it is therefore clinically relevant to investigate if upper GI disease affects the absorption of oral semaglutide.

In this study, the possible effect of inflamed stomach mucosa and/or an oesophageal disorder on the pharmacokinetics (PK), safety, and tolerability of oral semaglutide was investigated in subjects with T2D, and chronic gastritis and/or GERD.

2 | MATERIALS AND METHODS

2.1 | Study population

All subjects provided written informed consent. An independent ethics committee (Ärztekammer Nordrhein Körperschaft des öffentlichen Rechts Ethikkommission, Dusseldorf) reviewed and approved the protocol, consent form, and subject information sheets according to local regulations by appropriate health authorities (ethics approval ID number, 2016167; EudraCT number for the protocol, 2015-004534-10). The trial was conducted in accordance with Good Clinical Practice,[18] the Declaration of Helsinki,[19] and US Food and Drug Administration guidelines.[20]

Male or female subjects with T2D, aged 18-80 years, with a body mass index of 18.5-39.9 kg/m^2 and an HbA1c of 6.0%-9.0%, were included. The control group consisted of subjects with T2D without upper GI tract co-morbidities. Subjects in the group with upper GI disease had either chronic gastritis or GERD, or both. Each subject without upper GI disease was matched with respect to sex, age (±10 years), and body weight (±15.0 kg) to a subject in the group with upper GI disease (further information on the matching procedure is provided in the supporting information). Subjects were identified and diagnosed with chronic gastritis and/or GERD using a stepwise screening process. To increase the chance of identifying chronic gastritis in asymptomatic subjects, all subjects were screened for *Helicobacter pylori* (*H. pylori*) infection using the ^{13}C-urea breath test, with breath samples collected before and 30 minutes after ^{13}C-urea ingestion. Chronic gastritis diagnosis was based on a centralized histopathological examination of gastric mucosal biopsies collected at an oesophagogastroduodenoscopy (EGD) examination. All subjects underwent an EGD examination and histopathological examination of mucosal biopsies to confirm correct group assignment. Thus, the diagnosis of chronic gastritis was made independent of upper GI symptoms. The updated Sydney classification was used to describe the microscopic appearance of the stomach.[21] Chronic inflammation of at least mild intensity was required for a diagnosis of chronic gastritis. Subjects with a positive *H. pylori* breath test could be included in the trial because it was judged medically and ethically reasonable to postpone eradication treatment of *H. pylori* for subjects with no, or very limited, symptoms of infection until 24 hours after the last trial product administration. Subjects with GERD were identified by having symptoms of GERD and/or by findings of GERD at the EGD examination. The Los Angeles classification of oesophagitis was used to describe the extent of visible mucosal breaks of the oesophagus.[22] Subjects with upper GI disease were excluded if there were macroscopic findings at the EGD examination or microscopic findings upon examination of mucosal biopsies that indicated that immediate treatment or further medical investigations were required (e.g. oesophageal varices, obstructive stenosis, active bleeding, signs of malignancy).

A full list of eligibility criteria is detailed in Table S1. Key exclusion criteria included clinically significant, abnormal coagulation parameters and/or thrombocytes at screening indicating an increased bleeding risk; a history of major surgical procedures involving the stomach potentially affecting absorption of the trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery); renal impairment with an estimated glomerular filtration rate of less than 60 mL/min; and current treatment with anticoagulants, dual platelet inhibitors, antibiotics, and bismuth subsalicylate within 28 days of the first screening visit. It was anticipated that subjects with GERD would be using medications that could affect gastric pH, such as proton pump inhibitors (PPIs), and subjects with chronic gastritis would possibly be using PPIs and/or histamine H_2 receptor blocking drugs. Subjects who used drugs affecting gastric pH (e.g. PPIs, histamine H_2 receptor blocking drugs or antacids) on demand up to 2 days per week could participate in the study; however, subjects taking medications affecting gastric pH for more than 2 days per week were not allowed to participate to prevent any potential interactions.

2.2 | Study design

This was an open-label, parallel-group trial conducted at two sites in Germany from August 2016 to November 2017 (NCT02877355). All

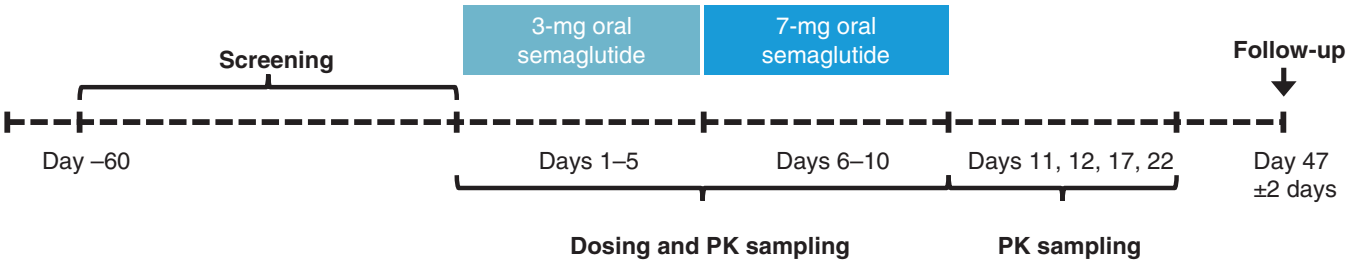

FIGURE 1 Study design. PK, pharmacokinetics

subjects were administered oral semaglutide 3 mg once daily for 5 days, followed by 7 mg for 5 days (Figure 1). Multiple-dose administration was selected to reduce the variability in semaglutide exposure.[23] Dose escalation was used to improve GI tolerability.[24] The 7 mg dose of oral semaglutide was chosen for ethical and operational reasons, as using the highest therapeutic dose of 14 mg would have led to a longer trial duration because of a two-step dose escalation, and thus a longer period withholding antibiotic treatment for *H. pylori*-positive subjects. The potential effect of upper GI disease on semaglutide exposure was not expected to be affected by the dose of semaglutide.

For all dosing days, subjects were not allowed to consume food or liquid (except water) for 6 hours before oral semaglutide dosing. Water was not allowed within 2 hours before dosing. Subjects continued fasting for 30 minutes after oral semaglutide administration.

Blood samples for semaglutide PK assessment were drawn on day 1 (pre- and post-dose), then pre-dose on days 6 to 10. Samples for SNAC PK analysis were drawn pre- and post-dose on days 1 and 10. On day 10, during the 10th dosing period, samples for semaglutide and SNAC PK analysis were taken at various time points up to 24 hours post-dose; samples were also collected for semaglutide PK analysis at 48, 168, and 288 hours post-dose. Plasma concentrations of semaglutide and SNAC were measured by liquid chromatography with tandem mass spectrometry, as previously described.[25]

At baseline, a ^{13}C-octanoic acid breath test[26] was performed to measure gastric emptying of a solid test meal and to determine if there were any differences between subjects with and without upper GI disease that could affect the interpretation of the PK findings.

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 hours after the 10th dose ($AUC_{0-24h,day10}$), between the two groups using a two-sided 95% confidence interval (CI) derived from the t-distribution. Using data from 119 healthy subjects from five clinical pharmacology trials with a similar 10-day design and similar dosing conditions, the estimate of the standard deviation (SD) of the logarithmic-transformed $AUC_{0-24h,day10}$ was 0.48. These trials had an end dose of 10 mg of oral semaglutide on day 10; for the sample size calculation it was assumed that the SD is the same for an end dose of 7 mg on day 10. It was also assumed that the SD for subjects with T2D is the same as for healthy subjects. With 24 evaluable profiles at the end of treatment in each group, assuming a SD for log ($AUC_{0-24h,day10}$) of 0.48, there was at least 80% probability to achieve a 95% CI for the ratio (R) of $AUC_{0-24h,day10}$ between the two groups within (0.73*R, 1.36*R). Because of the challenges in identifying subjects without upper GI disease, an amendment was made to the protocol that allowed the number in each group to be adjusted as needed, ensuring that the 80% probability was maintained. As a result, up to 60 subjects were planned to be enrolled to account for subjects being withdrawn from the trial.

The primary objective was to investigate if upper GI disease affects the PK properties of oral semaglutide in subjects with T2D. The primary endpoint, $AUC_{0-24h,day10}$ was log-transformed and analysed (SAS version 9.3) using an analysis of variance (ANOVA) model with age and logarithmic-transformed weight as continuous covariates, and group (two levels: with or without upper GI disease) and sex as fixed factors. The ANOVA model allowed for different variations in each of the two groups. The primary endpoint analysis was based on the full analysis set, which was defined as subjects who were exposed to at least one dose of the trial product. The mean difference in log-transformed $AUC_{0-24h,day10}$ between the two groups was estimated and back-transformed to the original scale, and presented as a ratio together with the corresponding two-sided 95% CI.

The secondary endpoint of maximum observed plasma concentration for semaglutide after the 10th dosing ($C_{max,day10}$) was analysed similarly. Time to maximum semaglutide concentration ($t_{max,day10}$) and half-life of oral semaglutide ($t_{½,day10}$) were summarized using descriptive statistics. The $t_{½,day10}$ of semaglutide was calculated as $\log(2)/\lambda_{z,sema,day10}$, where $\lambda_{z,sema,day10}$ is the terminal rate constant estimated by log-linear regression on the terminal part of the semaglutide concentration–time curve (up to 288 hours post-last dose) using at least three observations above the lower limit of quantification (LLOQ). If deemed relevant, the estimation of $\lambda_{z,sema,day10}$ took observations below LLOQ into account and used them as interval-censored observations.

The secondary objective was to investigate if upper GI disease affects the PK properties of SNAC in subjects with T2D. The supportive secondary endpoints, $AUC_{0-24h,day10}$ and $C_{max,day10}$ were analysed similarly to the primary endpoint and $t_{max,day10}$ was summarized using descriptive statistics.

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 (AEs), number of hypoglycaemic episodes, changes in laboratory safety variables, physical examination, vital signs and electrocardiogram.

3 | RESULTS

In total, 223 subjects were screened, 55 of whom (36 subjects with, and 19 without, upper GI disease) were included in the trial and exposed to oral semaglutide. Of these, 53 completed the trial: one subject with upper GI disease withdrew because of non-compliance with the protocol and one subject without upper GI disease withdrew consent. All 55 subjects were included in the full analysis and safety analysis set; the two subjects who withdrew from the trial did not complete the dosing regimen and were not eligible for inclusion in the PK analysis.

The mean age of the subjects was 62 years in the group with upper GI disease and 58 years in those without upper GI disease (Table S2). There was an even distribution of males and females between the two groups. Mean body weight was 92.3 kg in the upper GI disease group and 83.5 kg in the group without upper GI disease.

Of the 36 subjects with upper GI disease, there were eight (22%) subjects with GERD only, five (14%) subjects with chronic gastritis only, and 23 (64%) subjects with both GERD and chronic gastritis (Table S2). Nineteen subjects were asymptomatic for GERD according to protocol-defined criteria (i.e. no heartburn and/or regurgitation), of whom 14 showed signs of GERD during EGD and 15 were diagnosed with chronic gastritis after biopsy evaluation. Of the 31 subjects with a diagnosis of GERD, only 17 were symptomatic (Table S3). Of these 17 subjects, none were diagnosed with upper GI disease based on GERD

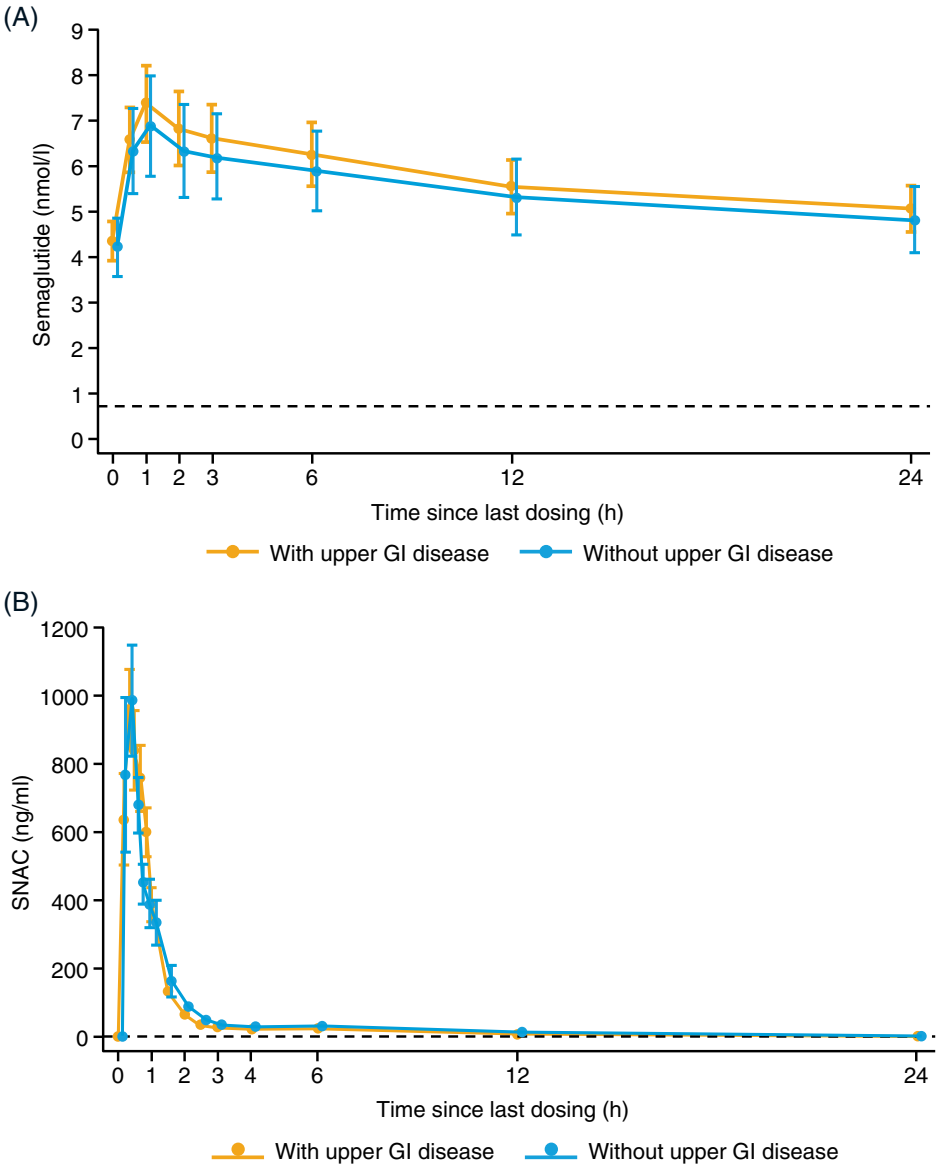

FIGURE 2 Geometric mean A, semaglutide, and B, SNAC concentration–time profiles during a 24-hour dosing interval after the 10th dose in subjects with or without upper GI disease. The dotted line represents the lower limit of quantification. Values below the lower limit of quantification are imputed. Error bars are ±SEM. GI, gastrointestinal; SEM, standard error of the mean; SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate

TABLE 1 Pharmacokinetic endpoints[a] of oral semaglutide and SNAC after the 10th dose

	Number of subjects in the full analysis set	N	Estimate	95% CI	*P* value
Semaglutide					
$AUC_{0-24h,day10}$ (nmol*h/L)					
Mean					
With upper GI disease	36	35	143.95	113.30, 182.88	
Without upper GI disease	19	18	122.05	89.51, 166.42	
Group ratio					
With/without upper GI disease			1.18	0.80, 1.75	.3986
$C_{max,day10}$ (nmol/L)					
Mean					
With upper GI disease	36	35	7.72	6.01, 9.90	
Without upper GI disease	19	18	6.63	4.76, 9.23	
Group ratio					
With/without upper GI disease			1.16	0.77, 1.76	.4629
SNAC					
$AUC_{0-24h,day10}$ (ng*h/ml)					
Mean					
With upper GI disease	36	35	1095.40	1012.80, 1184.73	
Without upper GI disease	19	18	1034.58	886.94, 1206.80	
Group ratio					
With/without upper GI disease			1.06	0.89, 1.26	.4999
$C_{max,day10}$ (ng/ml)					
Mean					
With upper GI disease	36	35	1120.61	870.74, 1442.19	
Without upper GI disease	19	18	1038.70	742.10, 1453.85	
Group ratio					
With/without upper GI disease			1.08	0.71, 1.65	.7171

Abbreviations: AUC, area under the plasma concentration–time curve; $AUC_{0-24h,day10}$, AUC from time 0 to 24 hours after the 10th dose; CI, confidence interval; C_{max}, maximum plasma concentration; $C_{max,day10}$, C_{max} after the 10th dose; GI, gastrointestinal; N, number of subjects with evaluable profiles; SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.

[a]$AUC_{0-24h,day10}$ and $C_{max,day10}$ were log-transformed and analysed in a linear normal model with age and log-transformed weight as continuous covariates and sex and group (two levels: with/without upper GI disease) as fixed effects; the model allowed for different variations in each of the two groups.

symptoms alone (i.e. all symptomatic patients showed findings of either GERD or chronic gastritis at the EGD examination or biopsy evaluation). Of the 28 subjects with chronic gastritis, 17 and 21 had mild chronic inflammation in the corpus and the antrum of the ventricle, respectively. Moderate chronic inflammation in the corpus and the antrum of the ventricle was present in two and seven subjects, respectively. No subjects had marked chronic inflammation (Table S4). Thirty subjects in the group with upper GI disease had abnormal macroscopic evaluation of the oesophagus, which was clinically significant in 25 patients. Seventeen subjects had grade A mucosal breaks and eight had grade B mucosal breaks; no subjects had grade C or D mucosal breaks. A total of 138 EGD examinations were performed. Out of the 223 screened patients, 14 were positive for *H. pylori*. Ten subjects with a positive *H. pylori* breath test were included in the trial, all in the upper GI disease group. Drugs affecting gastric pH were used by eight subjects at screening (PPI, n = 7; H_2-receptor antagonist, n = 1) and by three subjects during the 10-day treatment period (PPI, n = 2; sodium bicarbonate, n = 1; all taken as a single dose on day 7).

3.1 | Gastric emptying breath test

Gastric emptying breath test results performed at baseline indicated that the gastric emptying rate was similar between the groups (Figure S1), with mean gastric half-emptying times (SD) of 164 (30) and 176 (46) minutes for subjects with and without upper GI disease, respectively (Table S2). There was no correlation between gastric emptying rate and semaglutide exposure (data not shown).

TABLE 2 Selected[a] treatment-emergent adverse events by system organ class and preferred term

	With upper GI disease n (%) E	Without upper GI disease n (%) E
Number of subjects	36	19
Adverse events	24 (66.7) 77	10 (52.6) 16
GI disorders	15 (41.7) 37	3 (15.8) 6
Diarrhoea	8 (22.2) 10	1 (5.3) 1
Abdominal pain upper	4 (11.1) 4	1 (5.3) 1
Dyspepsia	4 (11.1) 5	0 (0.0) 0
Nausea	3 (8.3) 3	1 (5.3) 1
Vomiting	2 (5.6) 3	1 (5.3) 1
Abdominal discomfort	2 (5.6) 2	1 (5.3) 1
Abdominal pain	2 (5.6) 3	0 (0.0) 0
Flatulence	1 (2.8) 2	0 (0.0) 0
Abdominal distension	1 (2.8) 1	0 (0.0) 0
Abnormal faeces	0 (0.0) 0	1 (5.3) 1
Constipation	1 (2.8) 1	0 (0.0) 0
Eructation	1 (2.8) 1	0 (0.0) 0
Faeces hard	1 (2.8) 1	0 (0.0) 0
Toothache	1 (2.8) 1	0 (0.0) 0
Infections and infestations	6 (16.7) 8	3 (15.8) 3
Nasopharyngitis	6 (16.7) 7	3 (15.8) 3
Urinary tract infection	1 (2.8) 1	0 (0.0) 0
Metabolism and nutrition disorders	8 (22.2) 8	0 (0.0) 0
Decreased appetite	8 (22.2) 8	0 (0.0) 0
Nervous system disorders	3 (8.3) 3	3 (15.8) 3
Headache	3 (8.3) 3	3 (15.8) 3

Abbreviations: E, number of adverse events; GI, gastrointestinal; n, number of subjects with event.
[a]Total of events >10% by system organ class.

3.2 | Semaglutide pharmacokinetics

The geometric mean concentration–time profiles of semaglutide over 0–24 hours after the 10th dose are shown in Figure 2A. There was no statistically significant difference in total exposure to oral semaglutide in subjects with and without upper GI disease, with an estimated group ratio for $AUC_{0-24h,day10}$ of 1.18 (95% CI, 0.80, 1.75; $P = .40$) (Tables 1 and S5).

Geometric mean semaglutide concentration steadily declined for the remaining sampling period (up to 288 hours after dosing) (Figure S2A). The full semaglutide concentration−time profile from trial day 1 to day 22 is shown in Figure S2B. There was no statistically significant difference in $C_{max,day10}$ in subjects with and without upper GI disease, with an estimated group ratio of 1.16 (95% CI, 0.77, 1.76; $P = .46$; Tables 1 and S5). Other secondary endpoints were similar between the groups: median $t_{max,day10}$ (min; max) was 1.0 hours (0.0; 6.0) and 1.0 hours (0.5; 6.0) for subjects with and without upper GI disease, respectively. The geometric mean $t_{½,day10}$ (coefficient of variation) was 141 hours (11.6) and 142 hours (9.3) in subjects with and without upper GI disease, respectively.

3.3 | SNAC pharmacokinetics

The mean concentration–time profiles of SNAC over 0–24 hours after the 10th dosing are shown in Figure 2B. $AUC_{0-24h,day10}$ and $C_{max,day10}$ were similar in subjects with and without upper GI disease, with estimated group ratios of 1.06 (95% CI, 0.89, 1.26; $P = .50$) and 1.08 (95% CI, 0.71, 1.65; $P = .72$), respectively (Tables 1 and S5). The median $t_{max,day10}$ (min; max) for SNAC was 0.5 hours (0.17; 1.00) with upper GI disease and 0.33 hours (0.17; 1.00) without upper GI disease.

3.4 | Safety and tolerability

A total of 93 AEs were reported by 34 subjects (62%) across the two groups (77 events in 24 subjects in the group with upper GI disease; 16 events in 10 subjects in the group without upper GI disease) (Table 2). All AEs were mild (73) or moderate (20) in severity. The most frequently reported AEs were GI disorders (n = 43 in 18 subjects), including diarrhoea and upper abdominal pain, followed by infections and infestations (n = 11 in nine subjects), particularly nasopharyngitis (Table 2). A total of 51 AEs were considered probably, or possibly, related to oral semaglutide, and 29 of these events were GI disorders, while eight were attributable to decreased appetite. There were no AEs leading to withdrawal. Two serious AEs were reported: one event was upper abdominal pain in a subject with upper GI disease after initiating *H. pylori* eradication treatment; the other event involved hospitalization, after completing trial product administration, for a gastric polypectomy in a subject without upper GI disease after a polyp was discovered following the EGD performed during screening.

There were no reports of severe hypoglycaemic episodes, based on the American Diabetes Association classification of an event that requires the assistance of another person.[27] No clinically relevant changes in vital signs, laboratory parameters, physical examination or electrocardiogram were observed.

4 | DISCUSSION

As the stomach is the main absorption site for oral semaglutide and conditions affecting its integrity might affect absorption, this study examined whether upper GI disease could affect the exposure of oral semaglutide. Upper GI disease did not appear to influence semaglutide exposure after oral administration as there was no statistically significant difference in $AUC_{0-24h,day10}$ or $C_{max,day10}$ compared with those without upper GI disease. Similar to semaglutide exposure,

the AUC_{0-24h} and C_{max} of SNAC were comparable in subjects with and without upper GI disease.

The results of this study are supported by a population PK analysis of PIONEER trials, which showed that exposure of oral semaglutide for patients with upper GI disease fell within the bioequivalence interval for patients without upper GI disease.[28] In the current study, exposure of oral semaglutide was increased slightly, but not statistically significantly, in subjects with upper GI disease (group ratio for $AUC_{0-24h,day10}$ of 1.18). The plasma exposure-response relationships for oral semaglutide in the population PK analysis suggest that a comparatively small difference in exposure is unlikely to substantially affect the efficacy or safety of oral semaglutide.[28] Furthermore, in a study investigating the effect of omeprazole on the PK of oral semaglutide, a similar increase in semaglutide exposure was observed with oral semaglutide plus omeprazole compared with oral semaglutide alone, which was not considered to be clinically relevant given the broad therapeutic index of semaglutide.[29] Taken together, these data suggest that no dose adjustment is required when oral semaglutide is administered to patients with upper GI disease.

Body weight may influence oral semaglutide exposure, as indicated by a population PK analysis of PIONEER trials[28]; in that analysis, body weight was the covariate with the largest effect on oral semaglutide exposure, with increased exposure associated with low body weight. In the current study, mean body weight at baseline was approximately 9 kg greater in the upper GI disease group compared with the group without upper GI disease, yet exposure of oral semaglutide was increased slightly. Given the magnitude of the body weight difference (129 kg vs. 85 kg) to reduce exposure to a clinically relevant extent (ratio for exposure 0.75 [90% CI 0.71, 0.79]) in the population PK study,[28] the weight difference observed here was not considered likely to have a significant impact on interpretation of the data.

A strength of this study is that EGD was performed on all subjects to confirm the absence or presence of upper GI disease, and blinded biopsy evaluation was conducted in a centralized laboratory. There was a high prevalence of GERD in asymptomatic subjects with T2D, with signs of GERD in approximately three-quarters of asymptomatic patients. This is consistent with a previous study reporting that oesophageal reflux is frequently present in patients with diabetes and an increased prevalence of abnormal gastroesophageal reflux in patients with diabetes without symptoms of gastroesophageal disease versus the general population.[30] More subjects had histopathological confirmation of chronic inflammation than expected, despite a lack of symptoms and negative results with the *H. pylori* urea breath test. The prevalence of *H. pylori* infection in Europe is reported to be around 20%–40% and higher prevalence rates have been found in patients with T2D.[31-34] A small proportion of all screened subjects were positive for *H. pylori* in the present study as measured by the ^{13}C-urea breath test, which, while not 100% accurate, has been shown to have pooled sensitivity and specificity values of 96% and 93%, respectively, in meta-analyses.[35] The relatively high proportion of *H. pylori*-negative subjects showing signs of chronic inflammation suggests that alternative aetiologies may be responsible for the upper GI disease observed in this study population of T2D subjects, which could possibly be related to Western diet/habits and continuous use of multiple medications. The mechanisms responsible for the high prevalence of GI disorders seen here warrant further investigation. In addition, the prevalence of confirmed GERD/gastritis was shown to be high in symptomatic patients. As such, upper endoscopy should be considered for symptomatic patients.

Oral semaglutide, like other GLP-1RAs, may delay gastric emptying.[36] Moreover, patients with T2D have shown a tendency for delayed gastric emptying compared with healthy subjects in some, but not all, studies, which could potentially influence the bioavailability of oral semaglutide.[37,38] However, no significant difference was observed between the oral bioavailability of semaglutide in healthy subjects and patients with T2D based on a population PK model utilizing data from clinical pharmacology trials.[39] In the current study, gastric emptying rate was measured at baseline by a ^{13}C-octanoic acid breath test. This validated, non-invasive method uses a labelled short-chain fatty acid to indirectly measure gastric emptying, which is the rate-limiting step in the processing and excretion of ^{13}C-octanoic acid. There appeared to be no major differences in gastric emptying rate between subjects with or without upper GI disease.

Oral semaglutide was well tolerated in both groups. In line with previous findings with oral semaglutide, GI disorders were the most commonly reported AEs[6-12,23-25,29,40] and the overall safety profile was consistent with the GLP-1RA class.[2,41] As may be expected, relatively more AEs were reported in subjects with upper GI disease. Given the small sample size, the absence of a placebo group and the open-label trial design, the safety endpoints should be interpreted with caution. Furthermore, subjects with upper GI disease were, by definition, diagnosed with either chronic gastritis and/or GERD, which may have impacted AE reporting. A large assessment of the exposure-response relationship of oral semaglutide in the PIONEER trials indicates that upper GI disease has little influence on reports of nausea or vomiting, which appear to occur proportionate to circulating semaglutide concentrations.[28]

Although the highest therapeutic dose of oral semaglutide is 14 mg, it was considered sufficient to administer 7 mg for ethical and operational reasons. The potential effect of upper GI disease on semaglutide exposure was not expected to be affected by the dose of semaglutide, because oral semaglutide was administered at doses from 2.5 to 40 mg once daily in the phase II trial and was found to be clinically effective and well tolerated in a broad range of doses and exposures.[24]

Previous PK studies in subjects with a range of conditions (renal impairment, hepatic impairment, receiving omeprazole) have indicated a half-life for oral semaglutide after the 10th dosing in the range of 142–165 hours.[25,29,40] The $t_{½,day10}$ of oral semaglutide in the current study was found to be 141 and 142 hours in subjects with and without upper GI disease, respectively, which is at the lower end of this range but is still comparable with previous findings.

Regarding concomitant use of oral semaglutide with drugs affecting gastric pH that might be used in patients with upper GI disease, a previous study has shown that when oral semaglutide was administered with omeprazole in healthy subjects, there was no clinically relevant effect on semaglutide exposure.[29] In the current study, subjects were excluded if they used drugs affecting gastric pH (e.g. PPIs,

histamine H_2 receptor blocking drugs, antacids) for more than 2 days per week. Although permitted, no prokinetic agents were used in the trial.

Limitations of the current study include its open-label design. However, this is unlikely to have affected interpretation of PK endpoints, as all subjects received the same trial product and were included in the analysis, although the open-label design may have affected the reporting of AEs. Additionally, none of the enrolled subjects had severe upper GI disease, i.e. with marked chronic inflammation in the ventricle or grade C or D mucosal breaks in the oesophagus, indicating that the population included had a relatively low degree of severity for chronic gastritis or GERD. Another potential limitation is that only two upper GI diseases were investigated. Further trials would be useful to assess the effects of other upper GI diseases on the PK of oral semaglutide. The study had a limited sample size and exposure had not reached steady state by the time of the primary endpoint at day 10; however, a population PK analysis has been performed that supports the conclusion of the current study that upper GI disease has no clinically relevant impact on the exposure of oral semaglutide.[28]

In conclusion, there was no statistically significant difference in exposure of oral semaglutide in subjects with T2D with or without upper GI disease. As such, no dose adjustment for oral semaglutide is required in subjects with upper GI disease. Additional important findings were the high percentage of asymptomatic subjects with T2D with evidence of upper GI disease and the similar rate of gastric emptying between subjects with and without upper GI disease.

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CONFLICT OF INTEREST

JJM has received grants from MSD, Novo Nordisk, Sanofi, and lecture/other fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, MSD, Novo Nordisk, Sanofi, and Servier. CR is an employee and shareholder in Novo Nordisk. CG and AN are ex-employees and shareholders of Novo Nordisk. CK is an employee and co-owner of Profil, which has received research funds from several pharmaceutical and biotechnology companies. UH is an employee of Profil. LP-M has received payment or honoraria for lectures, presentations or educational events, and support for attending events from Novo Nordisk A/S and Eli Lilly. AT declares no competing interests.

AUTHOR CONTRIBUTIONS

CG: conception and design of the study. CG, AN, and CR: generation, collection, and assembly of data. All authors were involved in interpreting the data, drafting and revising the manuscript, and approving the final version of the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14632.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at novonordisk-trials.com. Data will be made available after research completion, and approval of the product and product use in the European Union and the USA. Individual participant data will be shared in data sets in a de-identified/anonymized format.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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