A trial to investigate the effect of oral semaglutide on the pharmacokinetics of furosemide and rosuvastatin in healthy subjects

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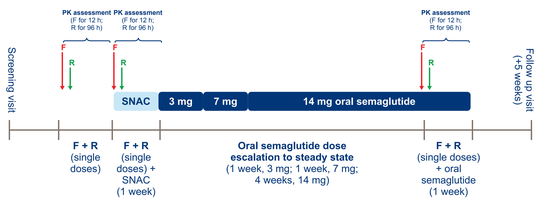
Introduction

- Oral semaglutide is a human glucagon-like peptide-1 (GLP-1) analogue co-formulated with an absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC, 300 mg), and is the first GLP-1 receptor agonist for oral administration.
- *In vitro* assessments have indicated that SNAC may inhibit drug transporters such as the breast cancer resistance protein (BCRP) and organic-anion-transporting polypeptides (OAT) OATP1B1 and OAT1/3 (data on file), potentially leading to increased plasma levels of drugs that are transporter substrates.
- Recent US FDA guidelines for clinical drug interaction studies list furosemide and rosuvastatin as relevant substrates for transporters BRCP and OATP1B1 and OAT 1 and/or 3[1,2].
- The objective was to investigate the effect of oral semaglutide on the pharmacokinetics (PK) of furosemide and rosuvastatin in humans.

Methods

- This was an open-label, one-sequence cross-over, single-centre, drug–drug interaction trial.
- Eligible subjects were healthy male and female volunteers, aged 18–65 years with a body mass index (BMI) between 20.0–29.9 kg/m² and HbA_{1c} <6.5%.
- Key exclusion criteria included any history of major surgery involving the stomach, potentially affecting absorption of the trial product and previous history of muscular toxicity with another statin or fibrate.
- The trial consisted of three treatment periods during which subjects received single doses of furosemide 40 mg and rosuvastatin 20 mg with a 24-h washout period in between:
  - Furosemide and rosuvastatin alone
  - Furosemide and rosuvastatin co-administered with SNAC 300 mg
  - Furosemide and rosuvastatin co-administered with oral semaglutide (Figure 1).
- Oral semaglutide was administered daily and dose escalated to steady state at week 6: treatment was initiated at 3 mg for 1 week, 7 mg for 1 week and then 14 mg for 4 weeks.
- Blood samples were collected at intervals over 12 h and 96 h for the measurement of plasma concentrations of furosemide and rosuvastatin, respectively.

Figure 1: Trial design.



F, furosemide; PK, pharmacokinetic; R, rosuvastatin; SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (300 mg).

Objectives

- The primary objective was to investigate the effect of oral semaglutide on the PK of furosemide and rosuvastatin.
- Secondary objectives were to investigate the effect of SNAC alone on the PK of furosemide and rosuvastatin and the safety and tolerability of oral semaglutide when co-administered with furosemide and rosuvastatin.

Statistical methods

- The primary endpoints were the area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty,SD}$) for single doses of furosemide and rosuvastatin.
- $AUC_{0-\infty,SD}$ of furosemide and rosuvastatin were log-transformed and analysed in a linear normal model with subject and oral semaglutide co-administration as fixed effects. No effect was concluded if the 90% confidence interval (CI) for the estimated treatment ratio of $AUC_{0-\infty,SD}$ for furosemide and rosuvastatin was within the pre-defined 'no effect' interval of 0.80 and 1.25.
- Supportive secondary endpoints included maximum plasma concentration (C_{max}) of furosemide and rosuvastatin (analysed similarly to the primary endpoint) and other PK parameters, such as time to maximum plasma concentration (t_{max}) and terminal half-life ($t_{½}$), analysed using descriptive statistics.

Results

Subjects

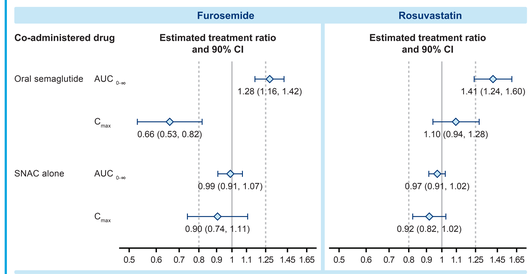
- The mean age (min; max) was 39 (18; 65) years, 76% of subjects were male and 76% were white.
- A total of 41 subjects were exposed to the trial product. Two subjects withdrew their consent after being exposed to the trial product for reasons not related to any adverse events (AEs).
- The remaining 39 subjects completed the trial and all 41 subjects were included in the full analysis set.
- Only subjects having evaluable furosemide or rosuvastatin profiles during both treatment periods were considered for evaluation. Due to technical issues with the laboratory, 6 samples were not analysed; therefore only 33 subjects were included in the statistical analysis for the rosuvastatin co-administered with oral semaglutide treatment period.

Pharmacokinetics

- When co-administered with oral semaglutide, the 90% CIs of the estimated treatment ratio for $AUC_{0-\infty,SD}$ for furosemide and rosuvastatin were not within the pre-defined 'no effect' interval. $AUC_{0-\infty,SD}$ for furosemide and rosuvastatin increased by 28% and 41%, respectively (Figure 2).
- When co-administered with oral semaglutide, a decrease in C_{max} of 34% was observed for furosemide and an increase in C_{max} of 10% was observed for rosuvastatin and the 90% CIs of the estimated treatment ratios were not within the pre-defined 'no effect' interval (Figure 2).
- Co-administration of SNAC alone had no effect on the $AUC_{0-\infty,SD}$ of furosemide or rosuvastatin, or on the C_{max} of rosuvastatin. A slight decrease (10%) was observed for the C_{max} of furosemide when co-administered with SNAC alone, with the 90% CIs of the estimated treatment ratios not being within the pre-defined 'no effect' interval (Figure 2).

Figure 2: Estimated treatment ratios of $AUC_{0-\infty,SD}$ and C_{max} of furosemide and rosuvastatin with and without co-administration of oral semaglutide and SNAC alone.

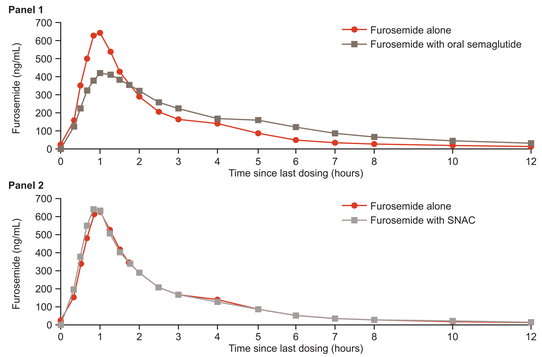
Key result



AUC, area under concentration–time curve; CI, confidence interval; C_{max}, time to maximum plasma concentration; ∞, infinity; SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.

- Mean plasma concentration–time profiles of furosemide and rosuvastatin with and without co-administration of oral semaglutide or SNAC are shown in Figure 3 and 4.

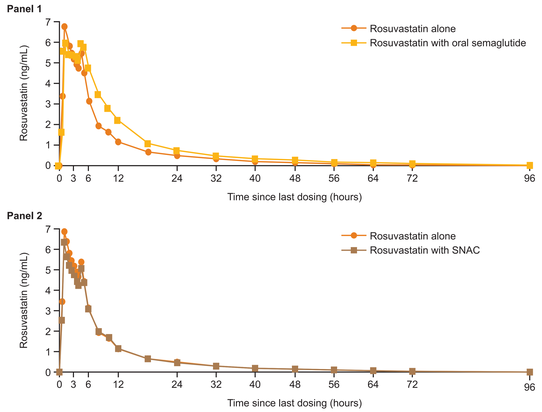
Figure 3: Geometric mean plasma concentration–time curves of furosemide with and without co-administration of oral semaglutide (panel 1) and SNAC alone (panel 2).



SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.

- The median t_{max} for furosemide and rosuvastatin was slightly later when co-administered with oral semaglutide (furosemide 1.3 h; rosuvastatin 1.5 h) compared with furosemide alone (0.9 h) and rosuvastatin alone (1.0 h). The median t_{max} of furosemide and rosuvastatin was similar when dosed alone and when co-administered with SNAC. Co-administration with oral semaglutide or SNAC alone had no effect on the $t_{½}$ of furosemide or rosuvastatin.

Figure 4: Geometric mean plasma concentration–time curves of rosuvastatin with and without co-administration of oral semaglutide (panel 1) and SNAC alone (panel 2).



SNAC, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate.

Only subjects having evaluable furosemide or rosuvastatin profiles during both periods (with/without oral semaglutide or SNAC) are included in the figures.

Safety and tolerability

- The most commonly reported AEs were gastrointestinal (GI) disorders, which are considered a class effect of GLP-1 receptor agonists. The majority of AEs were mild or moderate, with one severe event of abdominal pain being reported during the oral semaglutide alone period.
- There were no serious AEs, no unexpected AEs, no deaths and no AE leading to withdrawal from the trial.
- The safety and tolerability profile was consistent with previous GLP-1 receptor agonist trials[3,4].

Conclusions

- These data indicate that the SNAC component of oral semaglutide does not inhibit the transporters OAT1/3, BCRP and OATP1B1. Therefore, the changes in exposure and maximum concentrations of furosemide and rosuvastatin may be due to the known delayed gastric emptying effect of GLP-1 receptor agonists as previously oberseved[5,6], which could affect the rate and extent of absorption of co-administered drugs.
- The safety and tolerability profile of oral semaglutide was as expected for a GLP-1 receptor agonist and appeared to be well tolerated when co-administered with furosemide and rosuvastatin.
- These findings suggest that furosemide and rosuvastatin, which are commonly used in patients with type 2 diabetes, require no dose adjustment when co-administered with oral semaglutide.

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