2 Synopsis

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<th>Trial Registration ID-number</th>
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**Title of Trial**
A two-way cross-over, placebo-controlled interaction trial in two parts (in healthy subjects), studying liraglutide's potential influence on the absorption pharmacokinetics of lisinopril, atorvastatin, griseofulvin and digoxin, and liraglutide's potential influence on intragastric pH

**Investigator**
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**Trial Sites**
- Quintiles Phase I Unit, Strandbodgatan 1, SE-753 23 Uppsala, Sweden
- Quintiles Hermelinen, Varvsgatan 53, SE-972 33 Luleå, Sweden

**Publications**
None

**Trial Period**
29 May 2006 to 20 April 2007

**Development Phase**
Phase 1

**Objectives**

**Primary Objective:**
- To investigate if liraglutide at steady state changes AUC_{0-\infty} of atorvastatin, lisinopril, griseofulvin and digoxin

**Secondary Objectives:**
- To investigate if liraglutide at steady state changes C_{max} and t_{max} of atorvastatin, lisinopril, griseofulvin and digoxin
- To investigate if liraglutide changes intragastric pH
- To estimate the pharmacokinetics of liraglutide after a single dose and at steady state
- To assess the safety after administration of liraglutide in combination with atorvastatin, with lisinopril, with griseofulvin and with digoxin

**Methodology**
The trial was a randomised, double-blinded, placebo-controlled, two-way cross-over trial with two Parts (A and B) comparing the influence from liraglutide and placebo on the absorption PK of 40 mg atorvastatin and 20 mg lisinopril (Part A), 500 mg griseofulvin and 1 mg digoxin (Part B) and on intragastric pH (Part B). Volunteers in good general health were included in Part A, n = 42 and Part B, n = 28. Each subject attended 14 visits including a screening visit, three visits during liraglutide/placebo dose increase, two visits for pH measurements (in Part B) and liraglutide pharmacokinetics (in Parts A and B), four in-house visits of four days each when the drug-drug interaction (DDI) investigations were performed, and finally an End of Trial visit. The initiation of administration of liraglutide and randomisation of the subjects were performed at Visit 2. Liraglutide/placebo was administered daily in the morning with weekly increasing doses (0.6 mg, 1.2 mg and 1.8 mg) for 35 days each in random order in both cross-over periods.

The DDI investigations took place after the subject received either 1.8 mg liraglutide at steady state or placebo. In Part A one tablet (40 mg) atorvastatin and one tablet (20 mg) lisinopril were administered orally, and in Part B one tablet (500 mg) griseofulvin and one tablet (1 mg) digoxin were administered orally. The administration of the DDI drugs was timed in order that the C_{max} of liraglutide would coincide with absorption of the co-administered drugs. Sufficient wash-out periods of 9 days were allowed between the drug administrations. The total duration of the trial for each individual subject was up to 15 weeks.
Methodology continued

The investigation of intragastric pH (Part A) took place after the subject received either placebo or liraglutide at steady state on Day 20 in each cross-over period. pH was recorded every 4 seconds. Liraglutide or placebo was administered one hour after the start of measurement of pH which was then measured continuously for a further 23 h. The PK investigation of liraglutide (Part A and Part B) took place after the very first liraglutide dose and at steady state liraglutide. The first dose PK of liraglutide (0.6 mg) was assessed on Day 1 of each cross-over period. The steady state PK of liraglutide (1.8 mg) was assessed on Day 20 of each cross-over period. Blood sampling for PK of liraglutide took place for 24 h for both first dose and steady state liraglutide profiles.

Number of Subjects Planned and Analysed

- A total of 103 subjects were screened for Part A and Part B.
- Part A: 40 subjects were planned, 42 subjects were enrolled and treated, 6 subjects were withdrawn and 36 completed the trial.
- Part B: 30 subjects were planned, 28 subjects were enrolled and treated, 2 subjects were withdrawn and 26 completed the trial.

Diagnosis and Main Criteria for Inclusion

Healthy subjects between 18 and 55 years of age (both inclusive) with a BMI value of 18-30 kg/m² (both inclusive).

Test Product, Dose and Mode of Administration, Batch Number

- Liraglutide 3 mL FlexPen® (preparation of 6 mg/mL, batch numbers RQ50576 and RQ50390) was supplied by Novo Nordisk A/S. Liraglutide was administered as a s.c. injection in the abdomen in the morning.
- Atorvastatin (Lipitor®) 40 mg tablets (batch number 0279125 U)
- Lisinopril (Zestril®) 20 mg tablets (batch number CX529)
- Griseofulvin 500 mg tablets (batch number 001)
- Digoxin (Lenoxin®) 4 x 250 µg tablets (batch number 5K002)

Duration of Treatment

Liraglutide/placebo was administered daily in the morning with weekly increasing titration (0.6 mg, 1.2 mg and 1.8 mg) for 35 days each in random order in both cross-over periods. In Part A 40 mg atorvastatin was administered 5 h after placebo or liraglutide. Blood sampling for PK of atorvastatin took place for 72 h. 20 mg lisinopril was administered within 5 min after placebo or liraglutide. Blood sampling for PK of lisinopril took place for 60 h. In Part B 500 mg griseofulvin was administered at the same time as placebo or liraglutide. Blood sampling for PK of griseofulvin took place for 72 h. 1 mg digoxin was administered 7 h after placebo or liraglutide. Blood sampling for PK of digoxin took place for 72 h. The total duration of the trial for each individual subject was up to 15 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

- Liraglutide vehicle was used as placebo (batch numbers RQ50390 and SQ50209). Placebo was administered as s.c. injection in the abdomen in the morning.

Criteria for Evaluation – Efficacy

- Plasma concentration of atorvastatin
- Plasma concentration of lisinopril
- Plasma concentration of griseofulvin
- Serum concentration of digoxin
- Intragastric pH
- Plasma concentration of liraglutide

Criteria for Evaluation – Safety

- Adverse events
- Physical examination
- Vital signs
- ECG
- Hypoglycaemic episodes
- Clinical laboratory tests
### Statistical Methods

**Primary Endpoints**
- $\text{AUC}_{0-\infty}$ for atorvastatin, lisinopril and griseofulvin, and $\text{AUC}_{0-72h}$ for digoxin.
- $\text{AUC}_{0-\infty}$ for digoxin could not be calculated as the terminal elimination rate constant could not be estimated and this endpoint was replaced by $\text{AUC}_{0-72h}$.

For each of the four oral drugs the primary endpoint was log transformed and analysed using a linear normal model (ANOVA) with period and treatment as fixed effects and subject as a random effect.

For each of the four oral drugs the liraglutide treatment and the placebo treatment were declared equivalent with respect to $\text{AUC}_{0-\infty}$ if the 90% confidence intervals for the corresponding ratios of AUC were fully contained within the limits (0.80, 1.25).

**Secondary Endpoints**

**Pharmacokinetics of Atorvastatin, Lisinopril, Griseofulvin and Digoxin**
- $C_{\text{max}}$, $t_{\text{max}}$, $V_{z}/F$, CL/F, $\lambda_z$ and $t_{1/2}$ of atorvastatin, lisinopril and griseofulvin.
- $C_{\text{max}}$, $t_{\text{max}}$ and $\text{AUC}_{0-t}$ of digoxin.

For $C_{\text{max}}$, $V_{z}/F$, $t_{1/2}$ and $\text{AUC}_{0-t}$ similar analyses as for the primary endpoints were carried out. No statistical analysis of $\lambda_z$ or CL/F was performed. The analysis of $t_{\text{max}}$ was performed by use of a non-parametric method for paired samples.

**Intragastric pH Measurements**
The median pH in the different periods (entire 24 h, pre-dose, during meals, post-prandial and supine) was analysed using a linear normal model based on logarithmic transformed values with period and treatment as fixed effects and subject as a random effect. In addition, the fraction of pH measurements above 4 in the different periods was analysed using a linear normal model with period and treatment as fixed effects and subject as a random effect.

**Pharmacokinetics of liraglutide**
- $\text{AUC}_{0-24h}$, $C_{\text{max}}$ and $t_{\text{max}}$ after the first dose as well as $\text{AUC}_{\tau}$, $C_{\text{max}}$, $t_{\text{max}}$ and CL/F at steady state.
Dose adjusted $\text{AUC}_{0-24h}$ was compared to dose adjusted $\text{AUC}_{\tau}$ using a linear normal model based on the logarithmic transformed values. Period and state (first dose/steady state) were included as fixed effects and subject was included as a random effect. A similar method was used to analyse dose adjusted $C_{\text{max}}$ at steady state and at the initial dosing. The analysis of $t_{\text{max}}$ was performed by using a non-parametric method for paired samples.

**Safety**
All safety parameters were evaluated by use of summary statistics. No hypotheses were tested.

### Demography of Trial Population

- **Part A**: 42 healthy subjects (29 males and 13 females, 41 white and 1 other race) were included in the trial. Subjects were 28.7 ± 8.2 years of age with a mean body weight of 76.16 ± 10.86 kg and mean BMI 24.34 ± 2.99 kg/m².
- **Part A**: 28 healthy subjects (27 males and 1 female, all white) were included in the trial. Subjects were 25.8 ± 4.8 years of age with a mean body weight of 75.58 ± 8.22 kg and mean BMI 23.32 ± 2.38 kg/m².

### Efficacy Results

- For atorvastatin and griseofulvin, equivalence was demonstrated with respect to $\text{AUC}_{0-\infty}$ when the drugs were given at liraglutide steady state conditions compared to during placebo treatment.
- For lisinopril and digoxin, equivalence was not demonstrated with respect to $\text{AUC}_{0-\infty}$ (lisinopril) and $\text{AUC}_{0-72h}$ (digoxin) when the drugs were given at liraglutide steady state conditions compared to during placebo treatment. The $\text{AUC}_{0-\infty}$ for lisinopril was 15% lower (ratio 0.849 (90% CI: [0.747; 0.966])) and the $\text{AUC}_{0-72h}$ for digoxin was 16% lower (ratio 0.843 (90% CI: [0.722; 0.984])) at liraglutide steady state conditions compared to during placebo treatment.
- For atorvastatin, lisinopril, griseofulvin and digoxin, equivalence was not demonstrated with respect to $C_{\text{max}}$ when the drugs were given at liraglutide steady state conditions compared to during placebo treatment. $C_{\text{max}}$ for atorvastatin, lisinopril and digoxin were 38% lower (ratio 0.619 (90% CI: [0.533; 0.720])), 27% lower (ratio 0.730 (90% CI: [0.630; 0.846])) and 31% lower (ratio 0.691 (90% CI: [0.602; 0.794])) respectively. The $C_{\text{max}}$ for griseofulvin was 37% higher (ratio 1.369 (90% CI: [1.243; 1.507])) when administered at liraglutide steady state conditions.
Efficacy Results continued
- For atorvastatin, lisinopril and digoxin, $t_{\text{max}}$ was delayed by 1.25 h, 2.00 h and 1.125 h at liraglutide steady state conditions compared to during placebo treatment. For griseofulvin, $t_{\text{max}}$ was not affected by treatment.
- Median intragastric pH showed no statistically significant difference between liraglutide steady state conditions and placebo treatment for the entire period as well as during the supine, post-prandial and meal periods. Further, there was no difference in the fraction of intragastric pH values above 4 during the entire period, pre-drug, post-prandial or supine periods. For the meal period, the fraction of measured pH values above 4 was lower at liraglutide steady state conditions than during placebo treatment ($P = 0.044$).
- An expected increase in AUC$_\tau$ and C$_{\text{max}}$ was shown at steady state compared to single dose. The ratio of mean dose-adjusted AUC$_\tau$ at steady state and AUC$_{0-24h}$ after the first dose was 1.8. Liraglutide $t_{\text{max}}$ occurred 4 h earlier at steady state than at first dose (estimated median difference was -4 h (90% CI: [-5.5; -3.0]).

Safety Results
- More AEs were reported during treatment with liraglutide than during treatment with placebo. In addition, more AEs were judged to be related to trial product during treatment with liraglutide than during treatment with placebo.
- Gastrointestinal disorders, especially nausea, diarrhoea and vomiting were the predominant AEs reported after administration of liraglutide. Other AEs reported with increased frequency after administration of liraglutide compared to placebo included reduced appetite, weight loss, fatigue and sensation of coldness. Nervous system disorders, especially headache and dizziness were prevalent after administration of both liraglutide and placebo and occurred with similar frequency. Similar frequencies of nasopharyngitis were reported during liraglutide and placebo treatments.
- One SAE (pelvic fracture, unlikely related to treatment) was reported during treatment with placebo.
- There were no major differences between liraglutide and placebo treatment in AEs reported during atorvastatin, lisinopril griseofulvin or digoxin sampling.
- Increased transaminase was observed for one subject during placebo (subject was withdrawn) and 22 episodes of hypoglycaemia (19 minor and 3 with symptoms only) were reported. Eight of the episodes were reported during placebo treatment.

Conclusions
- The exposure (AUC) of single dose griseofulvin or atorvastatin was equivalent at steady state levels of liraglutide and during placebo treatment. Only a minor decrease in exposure of single dose lisinopril and digoxin was observed which was considered not clinically significant.
- The lower C$_{\text{max}}$ and delayed $t_{\text{max}}$ for the oral drugs when given concomitantly with steady state liraglutide was as expected reflecting a slight delay in gastric emptying.
- No significant overall effect of liraglutide on intragastric pH was recorded.
- Steady state pharmacokinetics for liraglutide showed increased AUC$_\tau$ and C$_{\text{max}}$ and earlier $t_{\text{max}}$ compared to single dose pharmacokinetics. The ratio between dose-adjusted AUC$_\tau$ at steady state and AUC$_{0-24h}$ after the first dose was approximately 1.8, indicating accumulation of liraglutide.
- No safety concerns were raised.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.