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Liraglutide 3.0 mg for Weight Management: A Population Pharmacokinetic Analysis

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Online Resource/Supporting Information

These supplementary data include a graphical covariate analysis to confirm the results of the population pharmacokinetic (PK) analysis, a description of the parameter estimates for the full PK model and a summary of the full PK model qualifications, including standard goodness-of-fit plots. The data also include figures illustrating the *post hoc* analysis of the effects of injection site on exposure, and the relation between creatinine clearance and liraglutide exposure.

Section S1. Qualification of the PK model.

The population PK model was qualified and found suitable for descriptive purposes and for use in exposure-response analysis in accordance with US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) guidelines as follows:

- The model fit was acceptable and there were no critical trends in the conditional weighted residuals vs. neither liraglutide concentration nor time.
- The individual clearance and volume of distribution estimates appeared to approximate normal distributions (data not shown).
- The model was able to describe exposure across subgroups of body weight and sex and for the three subgroups of glycaemic status.
- Whereas the shrinkage for apparent clearance (CL/F) was relatively low (23.9%), a larger shrinkage was found for apparent volume (V/F) (83.2%), indicating that model-derived individual estimates of V/F were relatively inaccurate. These findings imply that individual area under the curve (AUC) estimates were reasonably reliable, whereas individual maximum concentration (C_{max}) estimates were less reliable; they also suggest that there is limited information on covariates that influence volume of distribution. This is a consequence of the sparse sampling used for PK evaluation (only one sample at each PK visit). The shrinkage for the residual error was low (9.4%).
- The sensitivity of the model towards influential observations was investigated by excluding all records giving rise to weighted residuals above 4 or below -4, and re-estimating the models. In a separate run, obvious outlying concentrations including concentrations below 200 pM were excluded. The model was relatively robust towards both sets of exclusions. The largest deviations appeared for V/F.
- Sensitivity of the models towards changes in the fixed value of the absorption rate constant (K_A) was assessed by re-estimating the model with two alternative fixed values – plus and minus 25%, respectively. All parameters – except for V/F – were very insensitive towards changes of K_A values. The values of V/F ranged from 17.7 to 29.7 L when changing K_A by plus 25% and minus 25%, respectively. This was expected and was a consequence of the sparseness of data.
- A simplified linear mixed-effects analysis using individual drug concentrations disregarding PK sampling time after last dose was conducted and results were similar to the population PK analysis results.
- A visual predictive check showed that the model was able to reproduce the mean trend and the variability in the dataset used for estimation (not shown).

Section S2. Graphical covariate analysis.
The graphical covariate analysis comprised means and 95% confidence intervals of dose-normalised liraglutide concentrations versus time (expressed as binned time intervals), stratified by the following characteristics: dose (1.8/3.0 mg), body weight at baseline (minimum 60 kg; maximum 234 kg), age (<70 or ≥70 years), glycaemic status at baseline (normoglycaemia, prediabetes, type 2 diabetes). In addition, the interaction between sex and body weight for liraglutide exposure was also included in the graphical covariate analysis. The pre-specified age groups were <75 or ≥75 years, with the option of lowering the age cut-off by 5 or 10 years, if necessary, to ensure a sufficient number of subjects (n >20) in each age category. Therefore, in the final analysis, the age groups were <70 or ≥70 years. No other age categories were investigated, as previous data with liraglutide did not show any effect of age on liraglutide clearance.

Results

Dose-normalised liraglutide concentrations versus time after dose were similar following 1.8 mg and 3.0 mg doses (Figure S.1A), suggesting dose-proportional PK. It was therefore considered justified to conduct the graphical covariate data analysis using dose-normalised concentrations. As also shown in the Supporting Figure S.1, the graphical covariate data analysis revealed trends towards effects of sex, body weight and glycaemic status on liraglutide exposure. The effect of sex was similar in all four quartiles of body weight, suggesting that sex effects were not driven by body weight differences (Figure S.1B). Exposure appeared to decrease with increasing body weight and was lower in males than in females (Figure S.1C). Furthermore, a lower exposure appeared in individuals with diabetes compared to those with prediabetes or normoglycaemia (Figure S.1D).The remaining covariates (age, race and ethnicity) appeared to be without consistent effects on liraglutide exposure (data not shown).

Section S3: Assumptions and limitations of the PK model

Assumptions

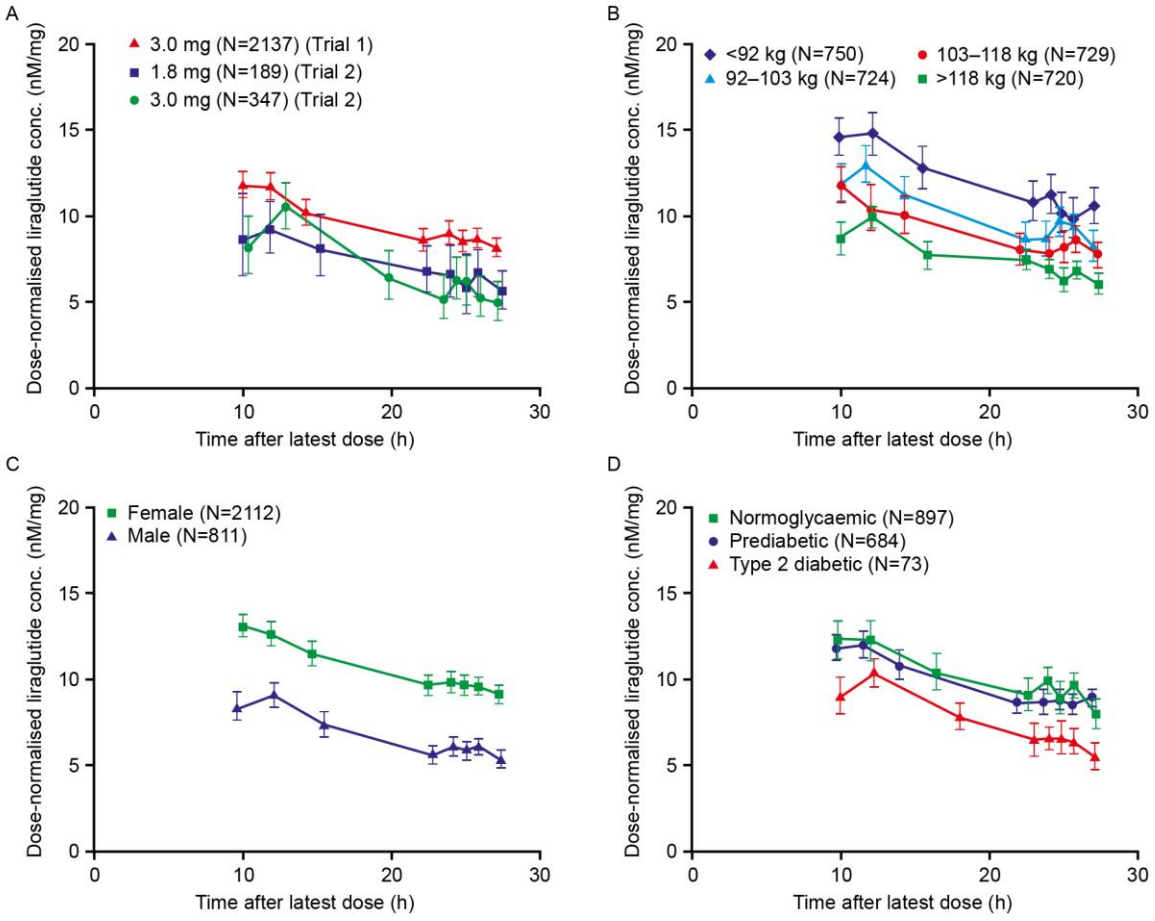
- The model was a one-compartment, linear, time-invariant, dose-proportional PK model with first order absorption. These assumptions were justified by adequate model fit to concentration-time course data. Although a more complex absorption model has been published for liraglutide, the current model is suitable for use with sparse data.[1-2]
- The assumption that individual post hoc estimates of CL/F were adequate for graphical analysis of the PK is justified by reasonable goodness-of-fit plots and limited shrinkage of clearance values.
- Differences between steady state concentration and actual concentration 3 days prior to a measurement was assumed to have negligible impact on the predicted concentration. This was justified by a plasma half-life of liraglutide of approximately 13 hours following subcutaneous administration.[3]
- PK values were assumed to be excluded at random and thereby to have limited impact on the results.

- Missing dosing information in Trial 3 was assumed not to influence the results of the dose-proportionality analysis. This was qualified by similar clearance values across trials.

Limitations

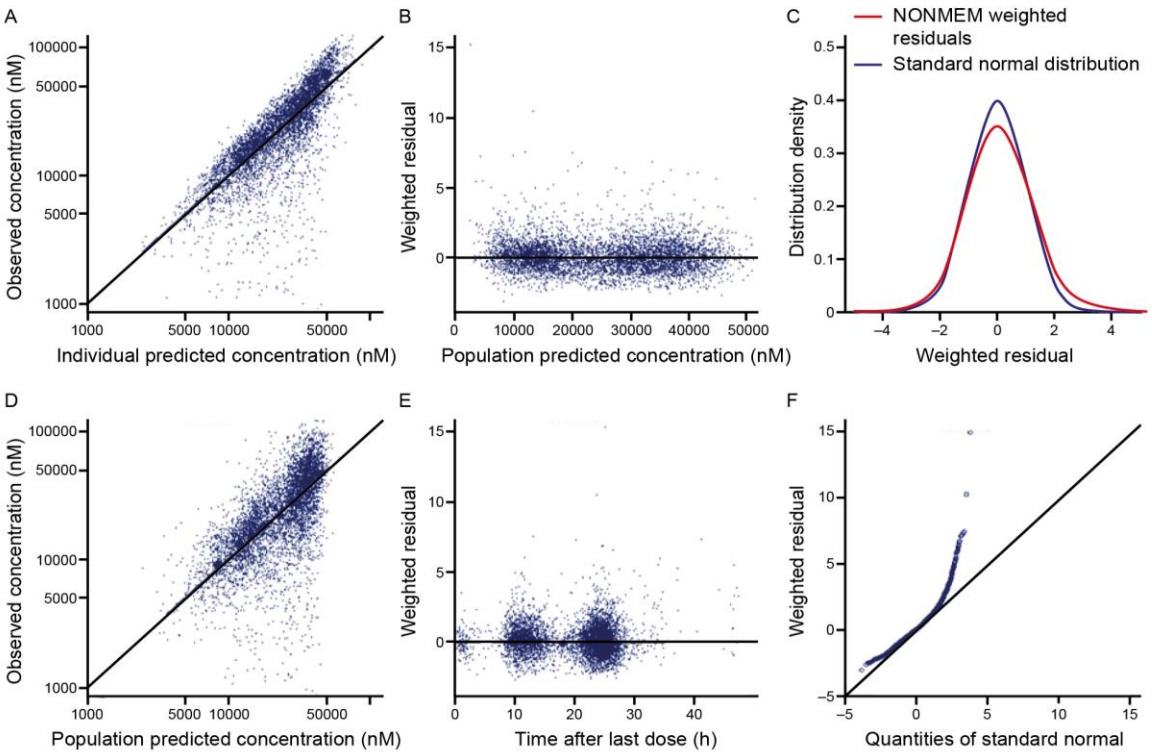
- Due to sparse PK sampling, limited information on volume of distribution was available, as seen in the high shrinkage. Therefore covariate effects on exposure were restricted to effects on clearance (and hence, AUC in this analysis). This was not considered a serious limitation due to low peak-to-trough variations for liraglutide.
- Assumptions about the structural PK model are believed to have little or no influence on the conclusions of this report. However, the shape of simulated concentration-time profiles obtained using the model may be slightly inaccurate.
- Due to a limited number of subjects in some covariate categories (e.g. number of subjects aged over 70 yrs; racial categories “Other” and “Asian”), covariate estimates are more uncertain for these categories. Despite this, the population PK analysis clearly demonstrates that these factors have limited impact..

Figure S1. Dose-normalised liraglutide concentration versus time since latest dose by A) dose, B) body weight, C) sex and D) glycaemic status.



Data are geometric means with 95% confidence interval (CI). N, number of subjects; nM/mg, nM liraglutide (serum concentration) per mg of liraglutide injected.

Figure S2. Goodness-of-fit plots for the population pharmacokinetic model.



A) Observed concentration versus individual predictions; B) weighted residuals versus population-predicted concentration; C) distribution of weighted residuals versus a standard normal distribution; D) observed concentration versus population predictions; E) weighted residuals versus time after last dose; F) quantile-quantile plot for the weighted residuals. NONMEM, non-linear mixed effect modelling.

Table S1. Parameter estimates from the full pharmacokinetic (PK) model with all covariate effects included.

Fixed effect parameters	Description	Unit	Estimate	% RSE	95% CI
$K_{A, Lira}$	Absorption rate constant (fixed)	1/h	0.09	N/A	N/A;N/A
CL/F_{Lira}	Apparent clearance	L/h	0.86	2	0.83-0.90
V/F_{Lira}	Apparent volume of distribution	L	24.60	9	20.3-28.8
Cov. weight	Exponent for effect of body weight	N/A	0.68	5	0.61-0.75
Cov. 1.8 mg	Coefficient for effect of dose	N/A	0.02	119	-0.03-0.08
Cov. male	Coefficient for effect of sex	N/A	0.27	6	0.24-0.30
Cov. age ≥70 years	Coefficient for effect of age	N/A	-0.10	45	-0.18-0.01
Cov. Black	Coefficient for effect of race	N/A	-0.09	26	-0.13-0.04
Cov. Asian	Coefficient for effect of race	N/A	-0.001	913	-0.09-0.08
Cov. Other	Coefficient for effect of race	N/A	-0.08	57	-0.17-0.01
Cov. Hispanic	Coefficient for effect of ethnicity	N/A	0.08	26	0.04-0.12
Cov. prediabetes	Coefficient for effect of glycaemic status	N/A	0.00	904	-0.05-0.06
Cov. diabetes	Coefficient for effect of glycaemic status	N/A	0.18	14	0.13-0.23
Random-effect parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**	
IIV – CL/F_{Lira}	Between-subject variability in CL/F	%CV	24.70	23.90	
IIV – V/F_{Lira}	Between-subject variability in V/F	%CV	34.70	83.20	
Residual error parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**	
Sigma	Residual error (proportional)	%CV	15.40	9.37	

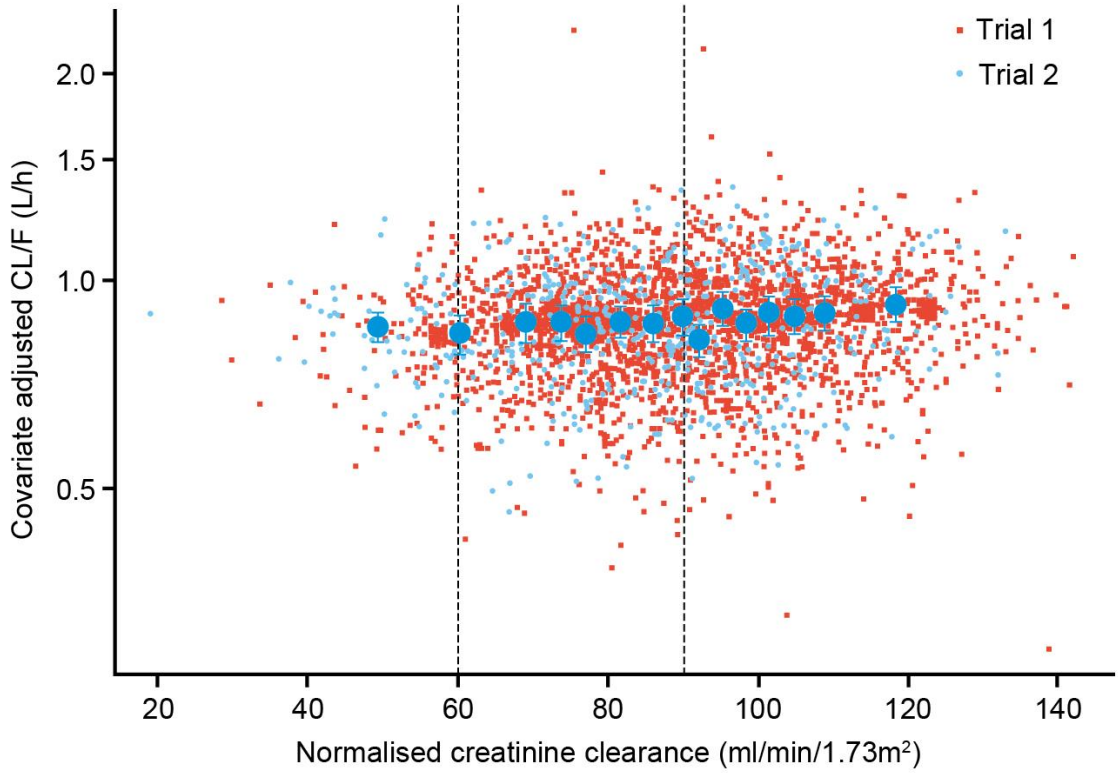
Covariate parameters were log-transformed for the estimation,e.g. E_male=exp (Cov.male). CI, confidence interval; CL/F, apparent clearance; Cov., covariate; CV, coefficient of variation; K_A, absorption rate constant; Lira, liraglutide; N/A, not applicable; RSE, relative standard error; V/F, apparent volume of distribution.

Table S2. Baseline characteristics for the phase-2 dose-finding trial used in the validation of dose-proportionality of liraglutide 1.2 mg to 3.0 mg.

Covariate		Liraglutide dose				
		1.2 mg	**1.8 mg**	**2.4 mg**	**3.0 mg**	**Total**
	N	88	79	79	85	331
Sex	Female, N (%)	66 (75)	59 (75)	61 (77)	63 (74)	249 (75)
	Male, N (%)	22 (25)	20 (25)	18 (23)	22 (26)	82 (25)
Age, years	Mean (SE)	48 (9)	46 (10)	45 (11)	46 (11)	47 (10)
Race	White, N (%)	87 (99)	78 (99)	78 (99)	84 (99)	327 (99)
	Black or African-American, N (%)	0 (0)	1 (1)	0 (0)	1 (1)	2 (0.5)
	American Indian or Alaskan native, N (%)	1 (1)	0 (0)	1 (1)	0 (0)	2 (0.5)
Body weight, all subjects, kg	Mean (SE)	97 (13)	98 (12)	100 (12)	97 (14)	98 (13)
BMI, kg/m^2	Mean (SE)	35 (3)	35 (3)	35 (3)	35 (3)	35 (3)

BMI, body mass index; N, number of subjects; SE, standard error.

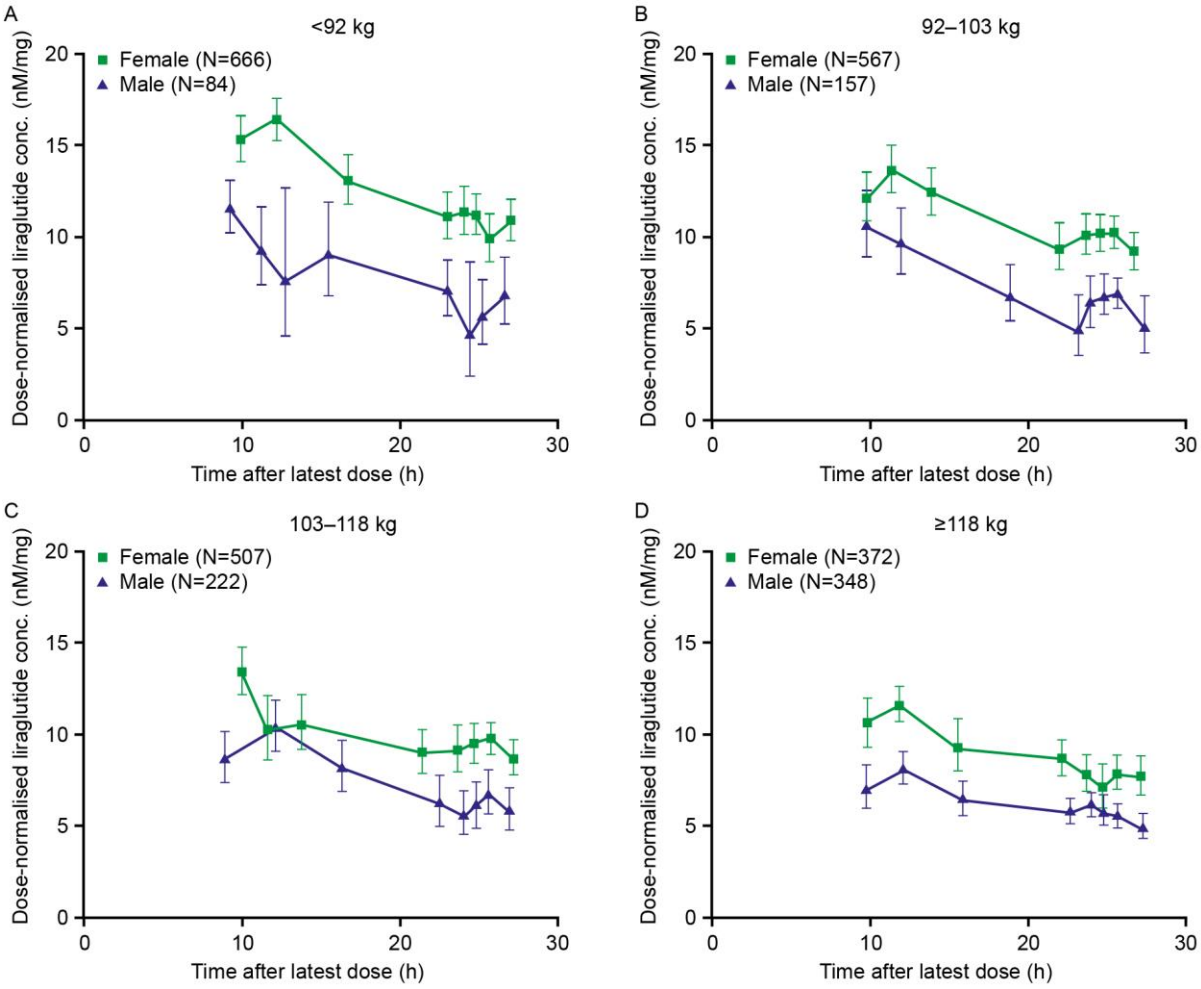
Figure S3. Individual covariate-adjusted values for liraglutide clearance (CL/F) versus baseline creatinine clearance.



Trial 1: SCALE Obesity and Prediabetes trial[4]

Trial 2: SCALE Diabetes trial[5] Data are individual and geometric mean values with 95% CI for each quantile of normalised creatinine clearance estimated from creatinine concentrations in serum. The vertical lines indicate the boundaries between normal renal function and mild and moderate renal impairment, respectively. CI, confidence interval; CL/F, apparent clearance.

Figure S4. Model-derived mean dose-normalised liraglutide concentrations versus time since latest dose overlaid on observed data by sex and body weight quartiles (A-D).



Data are geometric means with 95% CI. Time values are grouped as quantiles. CI, confidence interval; Conc., concentration; Lira, liraglutide; nM/mg, nM liraglutide (serum concentration) per mg of liraglutide injected.

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