Electronic Supplemental Material (Online Resource)

Journal: *Clinical Pharmacokinetics*

Comparable liraglutide pharmacokinetics in pediatric and adult populations with type 2 diabetes: a population pharmacokinetic analysis

Kristin C. Carlsson Petri[1], Lisbeth V. Jacobsen[1], David J. Klein[2]

[1]Novo Nordisk A/S, Søborg, Denmark

[2]Medpace, Cincinnati, OH, USA

Correspondence: Kristin C. Carlsson Petri, Quantitative Clinical Pharmacology, Novo Nordisk A/S, 108-110 Vandtårnsvej , Søborg, DK-2860, Denmark. Tel: +45 4444 8888. Email: KCC@novonordisk.com

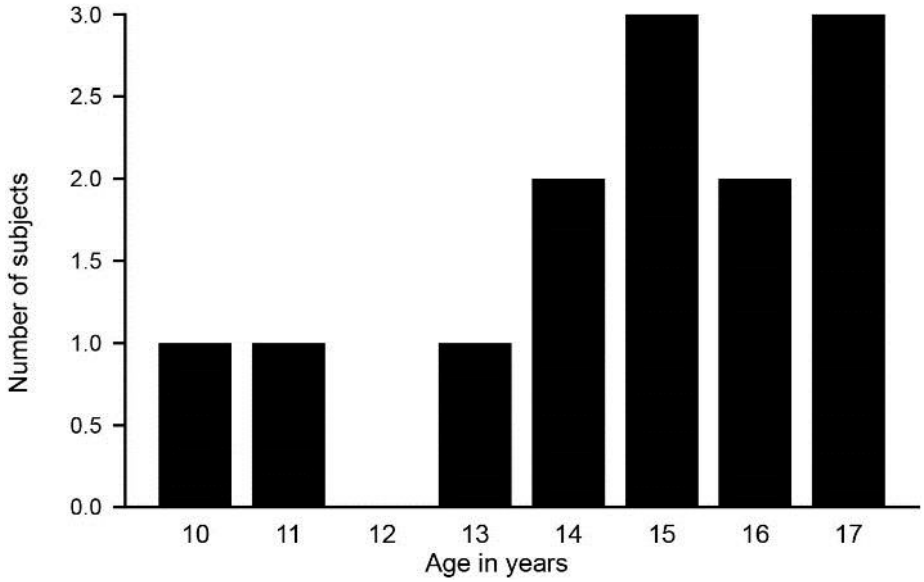

Figure 1. Age distribution in the pediatric population (Trial 1). X-axis: age in years. Y-axis: number of subjects.

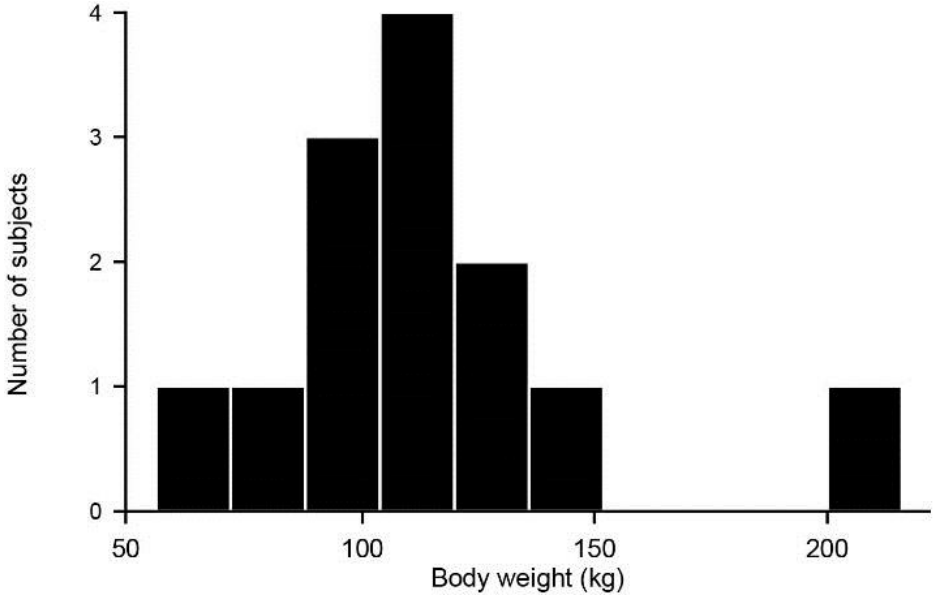

Figure 2. Body weight distribution in the pediatric population (Trial 1). X-axis: body weight in kg. Y-axis: number of subjects.

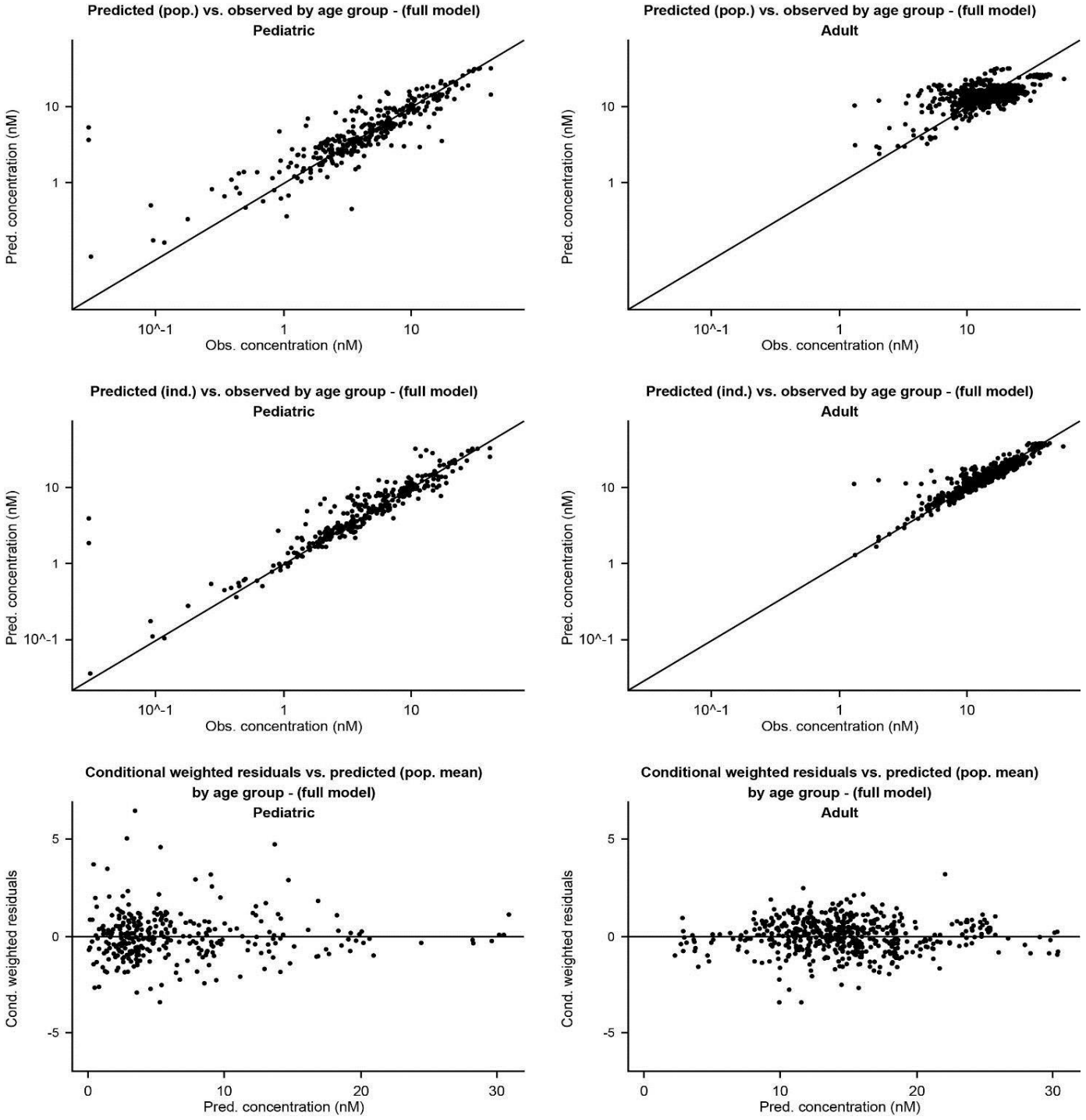

Figure 3. Population and individual predicted values vs. observed values and conditional weighted residuals vs. predicted values for the full model split between pediatric and adult subjects. Cond., conditional; ind., individual; Obs., observed; pop., population; Pred., predicted.

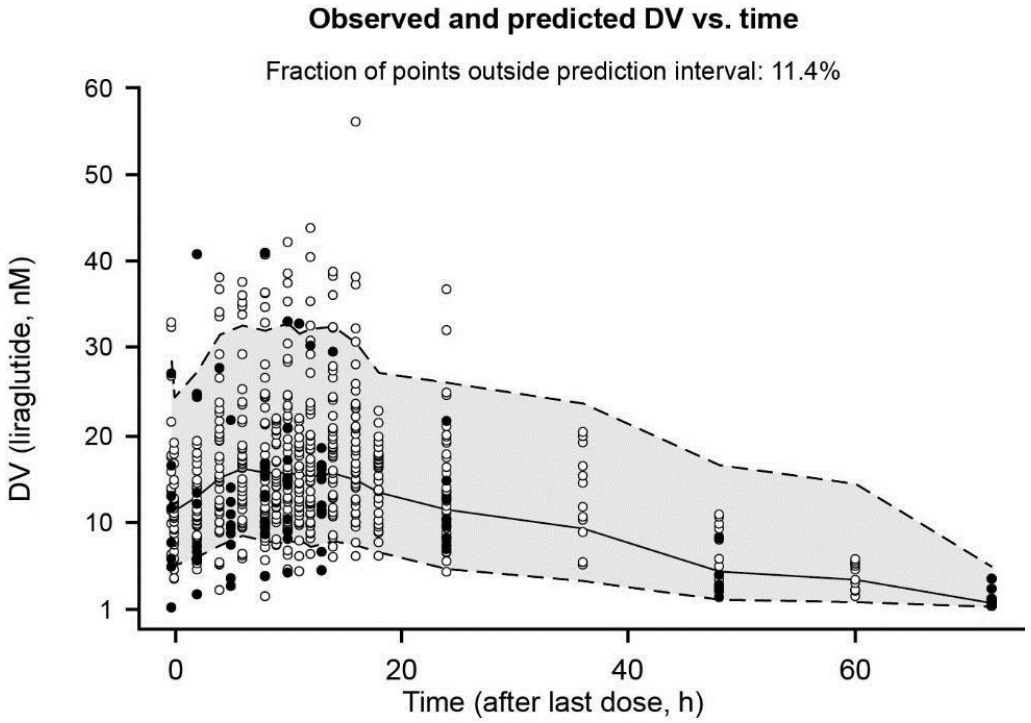

Figure 4. Visual predictive check for the full model. Liraglutide concentration (nM) vs. nominal time since last dose (h). Circles show the observed steady-state concentrations for subjects receiving 1.8 mg once-daily (pediatric subjects: black filled circles; adult subjects: open circles). The lines and shaded area show the median and 90% prediction interval. The observations at nominal time points at 5, 9 and 13 h have been binned with the observations at 4, 8 and 12 h, respectively, due to a low number of observations at these time points. DV, dependent variable.

Table 1. Parameter estimates of the full and base models

Fixed-effects parameters	**Description**	**Unit**	**Full model**		**Base model**	
			Estimate	**Uncertainty RSE (%)**	**Estimate**	**Uncertainty RSE (%)**
K_A	Absorption rate constant	L/h	0.0657	6	0.0657	7
CL/F	Apparent clearance	L/h	1.06*	10	1.49	9
V/F	Apparent volume of distribution	L	15.3	19	18.1	15
F	Bioavailability	1	1 (fixed)	N/A	1 (fixed)	N/A
Cov CL-BWT	CL body weight exponent**	N/A	0.929	15	N/A	N/A
Cov CL-Gen	CL – gender contrast**	N/A	0.365	29	N/A	N/A
Cov CL-AGEgr	CL- age category contrast**	N/A	0.107	91	N/A	N/A
Random-effects parameters	**Description**	**Unit**	**Estimate**	**Shrinkage (%)**	**Estimate**	**Shrinkage (%)**
CL/F (dose 1.8 mg)	BSV in CL/F	% CV	34	1	48	11
Residual error parameters	**Description**	**Unit**	**Estimate**	**Shrinkage (%)**		
Sigma	Residual error (proportional)	% CV	23	7	23	8

BSV, between subject variability; CV, coefficient of variation; RSE, relative standard error.

*Reference value corresponding to an adult female subject weighing 90 kg.

**Expression for CL/F:

$$\frac{CL_i}{F} = \frac{CL}{F} * \left(\frac{BWT}{90kg} \right)^{CovCLBWT} * e^{CovCLGen\{ifmale\}} * e^{CovCLPaed\{ifpaediatric\}} * e^{(\eta_i)}$$