Supplementary Online Material

Title: A randomized trial investigating the pharmacokinetics, pharmacodynamics and safety of subcutaneous semaglutide once-weekly in healthy male Japanese and Caucasian subjects

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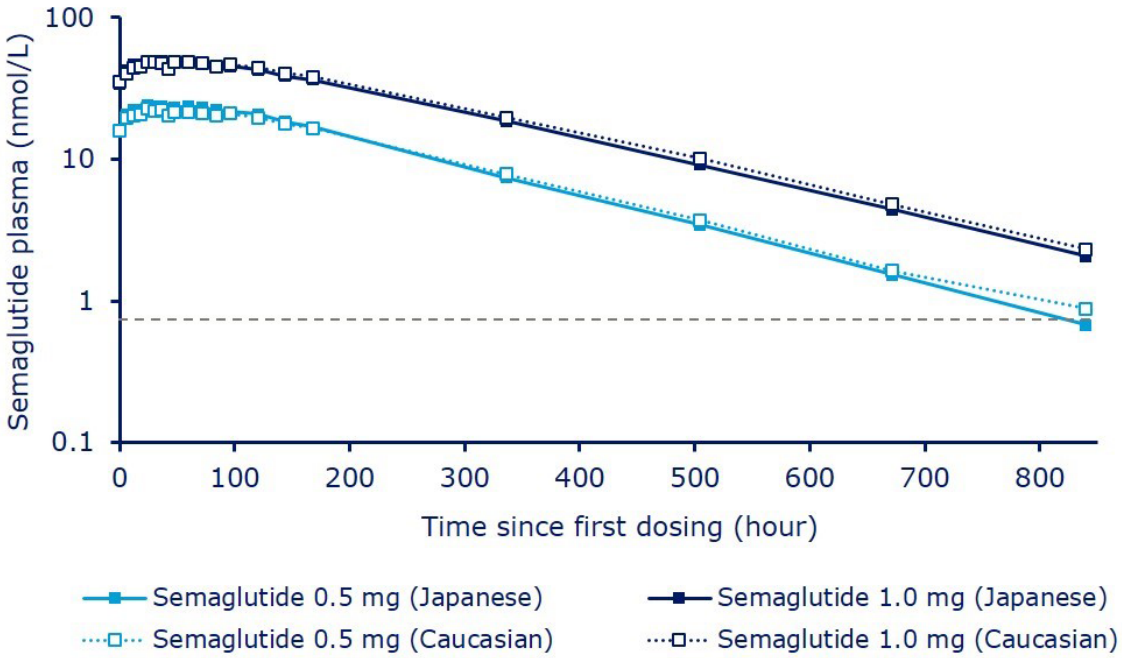
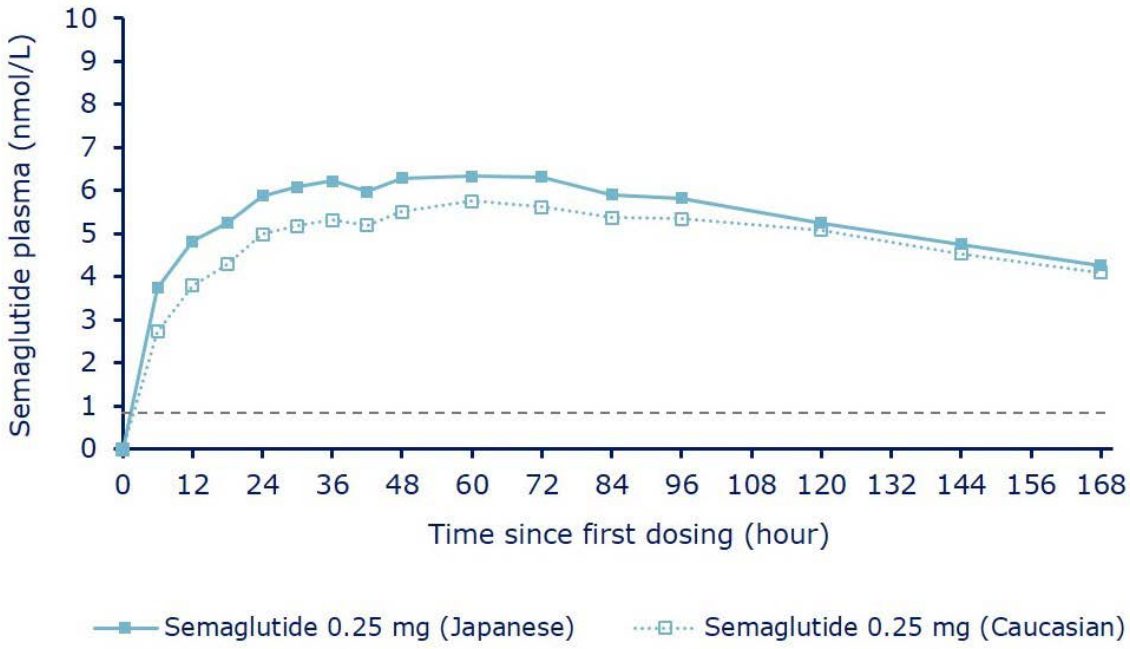
Figure legends

Supplementary Figure S1. *Mean semaglutide profile at steady state: 0−840 hours after the last dose*



Values are geometric means, plotted on a logarithmic scale. All values below the lower limit of quantification (dashed line) are imputed. Terminal elimination half-life ($t_{½}$) was derived from the terminal part of concentration–time curves after the last dose.

Supplementary Figure S2. *Mean semaglutide profile after the first dose: 0–168 hours*



Values are arithmetic means. Note: the initial dose was 0.25 mg for all subjects receiving semaglutide. The dashed line indicates the lower limit of quantification.

Supplementary Table S1. *Statistical analysis of pharmacokinetic endpoints after first dose*

	Japanese subjects (n=16)	**Caucasian subjects (n=16)**	**Estimated race ratio [95% CI] (Japanese:Caucasian)**
$AUC_{0-168h,sema,SD}$ (nmol*h/L)	895 (14.6)	804 (17.7)	1.11 [0.99; 1.25]
$C_{max,sema,SD}$ (nmol/L)	6.8 (17.2)	6.0 (20.4)	1.14 [1.00; 1.30]
$t_{max,sema,SD}$ (h)†	48 [24; 84]	60.0 [36; 144]	-

Values are geometric means (CV) and estimated race ratios [95% CI]. †Values are median [minimum; maximum]. The endpoint is logarithmic transformed and analyzed in a linear normal model with race as a fixed factor. AUC, area under the curve; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation (%); SD, single dose; t_{max}, time to maximum concentration.

Supplementary Table S2. *Statistical analysis of pharmacodynamic endpoints of semaglutide*

	Japanese subjects				**Caucasian subjects**			
	ETD Semaglutide 0.5 mg – placebo [95% CI]	**p-value**	**ETD Semaglutide 1.0 mg – placebo [95% CI]**	**p-value**	**ETD Semaglutide 0.5 mg – placebo [95% CI]**	**p-value**	**ETD Semaglutide 1.0 mg – placebo [95% CI]**	**p-value**
Body weight (kg)	–2.42 [–4.46; –0.39]	≤0.05	–6.06 [–8.10; –4.02]	≤0.05	–4.30 [–6.52; –2.08]	≤0.05	–8.28 [–10.55; –6.01]	≤0.05
Fasting plasma glucose (mg/dL)	–10.8 [–19.7; –1.9]	≤0.05	–12.9 [–21.7; –4.1]	≤0.05	–0.8 [–9.4; 7.8]	>0.05	–9.7 [–18.8; –0.5]	≤0.05
(mmol/L)	–0.60 [–1.10; –0.10]	≤0.05	–0.72 [–1.20; –0.23]	≤0.05	–0.04 [–0.52; 0.004]	>0.05	–0.54 [–1.04; –0.03]	≤0.05
	ETR Semaglutide 0.5 mg:placebo [95% CI]	**p-value**	**ETR Semaglutide 1.0 mg:placebo [95% CI]**	**p-value**	**ETR Semaglutide 0.5 mg:placebo [95% CI]**	**p-value**	**ETR Semaglutide 1.0 mg:placebo [95% CI]**	**p-value**
Fasting insulin (pmol/L)	1.38 [0.77; 2.47]	>0.05	1.13 [0.63; 2.03]	>0.05	1.07 [0.59; 1.96]	>0.05	0.77 [0.41; 1.43]	>0.05
Fasting C-peptide (nmol/L)	1.43 [0.95; 2.14]	>0.05	1.26 [0.83; 1.89]	>0.05	0.94 [0.61; 1.45]	>0.05	0.82 [0.52; 1.29]	>0.05
Fasting glucagon (pg/mL)	1.02 [0.78; 1.33]	>0.05	0.86 [0.66; 1.12]	>0.05	0.96 [0.73; 1.26]	>0.05	0.88 [0.67; 1.17]	>0.05
Fasting pro-insulin (pmol/L)	0.96 [0.56; 1.63]	>0.05	0.63 [0.37; 1.09]	>0.05	1.07 [0.62; 1.84]	>0.05	0.75 [0.41; 1.37]	>0.05

Values are estimated treatment differences [95% CI] or estimated treatment ratios [95% CI]. The endpoint is analyzed by a mixed model for repeated measurements where all post baseline measurements obtained at planned visits until end of treatment enter as the dependent variables, and visit, dose group, race and race-by-dose group interaction are included as fixed factors and baseline value as covariate. Furthermore, interaction terms of visit-by-dose group, visit-by-race, visit-by-race-by-dose group and visit-by-baseline value were included. Fasting insulin, C-peptide, glucagon and pro-insulin were logarithmically transformed and analyzed. CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio.

Supplementary Table S3. *Adverse event summary*

	Japanese subjects									Caucasian subjects								
	Semaglutide 0.5 mg			**Semaglutide 1.0 mg**			**Placebo**			**Semaglutide 0.5 mg**			**Semaglutide 1.0 mg**			**Placebo**		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Number of subjects	8			8			6			8			8			6		
Adverse events	6	(75.0)	8	5	(62.5)	13	1	(16.7)	1	4	(50.0)	6	5	(62.5)	12	2	(33.3)	2
Severity																		
Moderate	1	(12.5)	2	0			0			2	(25.0)	2	1	(12.5)	3	0		
Mild	5	(62.5)	6	5	(62.5)	13	1	(16.7)	1	3	(37.5)	4	4	(50.0)	9	2	(33.3)	2
By system organ class†																		
Gastrointestinal disorders	5	(62.5)	6	3	(37.5)	9	1	(16.7)	1	2	(25.0)	4	2	(25.0)	5	0		
Metabolism and nutrition disorders	0			3	(37.5)	3	0			0			3	(37.5)	3	0		

Adverse events include events that occurred from first exposure to the follow-up visit. †Frequently reported adverse events (≥3 subjects) are shown by system organ class.
E, number of events; N, number of subjects; %, proportion of subjects.