

Supplementary Material

Clinical Pharmacokinetics

Systemic Pharmacokinetic Principles of Therapeutic Peptides

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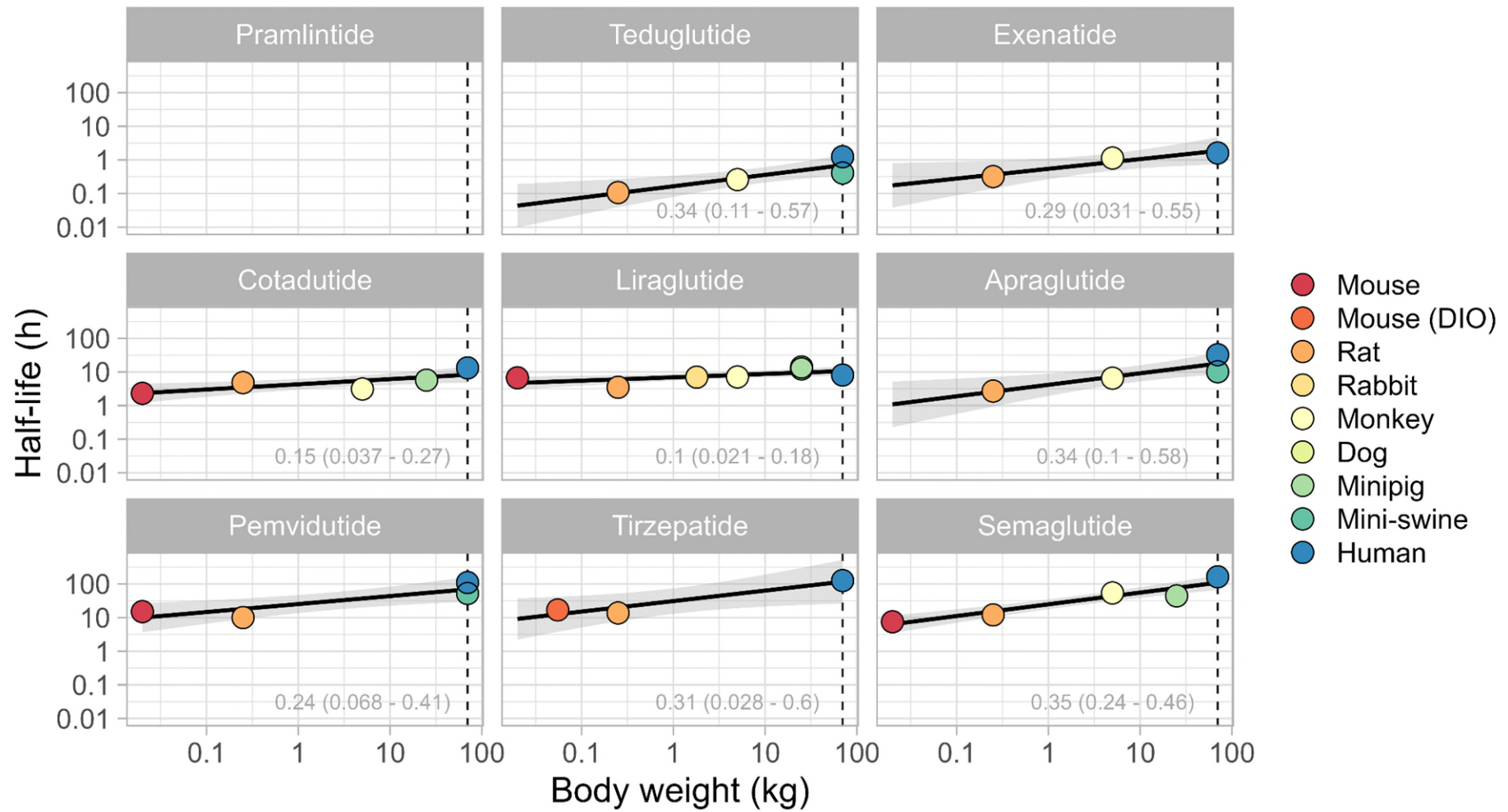


Fig. S1. Allometric plots of half-life for the considered peptides. Linear regression with 80% confidence range is indicated by line and shaded area (estimated allometric slope indicated bottom-right). Vertical line indicates 70 kg human body weight. DIO: diet-induced obese.

Tables

Table S1. Details of pharmacokinetic data with estimates of CL/F , V_d/F , $t_{1/2}$ and plasma protein binding (PPB) for the evaluated therapeutic peptides across species. NCA: Noncompartmental Analysis; CMA: Compartmental Model Analysis.

Peptide	Species	CL/F (mL/h/kg)	Source / dose / analysis	V_d/F (L/kg)	Source / dose / analysis	Half-life (h)	Source / dose / analysis	Bio- availability	Source / dose / analysis	Fraction unbound	Source
Semaglutide	Mouse	19	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA (dose/AUC)	0.21	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	7.5	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA	-	-	0.27%	AstraZeneca data on file.
	Rat	10	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA (dose/AUC)	0.18	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	12	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA	-	-	0.27%	AstraZeneca data on file.
	Monkey	1.6	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA (dose/AUC)	0.13	Regulatory documentation [1] / s.c. repeat dose-norm to 1 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	54	Regulatory documentation [1]. NCA estimate.	-	-	0.10%	AstraZeneca data on file.
	Minipig	1.7	Literature [2] / single s.c 2 nmol/kg; single i.v. 2 nmol/kg / NCA	0.11	Literature [2] / single s.c 2 nmol/kg; single i.v. 2 nmol/kg / NCA (V_z/F_{sc})	44	Literature [2] / single s.c 2 nmol/kg; single i.v. 2 nmol/kg / Calculated ($\ln(2)/(CL/F)*(V_d/F)$)	94%	Literature [2] / single s.c 2 nmol/kg; single i.v. 2 nmol/kg / NCA	-	-
	Human	0.57	Literature [3] / Multiple clinical trials 0.25 – 1.5 mg / CMA (population approach)	0.14	Literature [3] / Multiple clinical trials 0.25 – 1.5 mg / CMA (population approach)	160	Literature [3] / Multiple clinical trials 0.25 – 1.5 mg / CMA (population approach). Calculated as $\ln(2)/(CL/F)*(V_d/F)$	85%	Literature [3] / Multiple clinical trials 0.25 – 1.5 mg / CMA (population approach).	0.25%	AstraZeneca data on file.
Tirzepatide	Mouse (DIO)	11	AstraZeneca data on file / single s.c 10 nmol/kg; single i.v. 10 nmol/kg / CMA	0.26	AstraZeneca data on file / single s.c 10 nmol/kg; single i.v. 10 nmol/kg / CMA	17	AstraZeneca data on file / single s.c 10 nmol/kg; single i.v. 10 nmol/kg / CMA	72%	AstraZeneca data on file / single s.c 10 nmol/kg; single i.v. 10 nmol/kg / CMA	0.41%	AstraZeneca data on file.

Cotadutide	Rat	8.6	AstraZeneca data on file / single s.c 10 nmol/kg / NCA	0.17	AstraZeneca data on file / single s.c 10 nmol/kg / NCA	14	AstraZeneca data on file / single s.c 10 nmol/kg / NCA	-	-	0.39%	AstraZeneca data on file.
	Human	0.71	Literature [4]. Repeat dose 0.5 – 10 mg / NCA	0.13	Literature [4]. Repeat dose 0.5 – 10 mg / NCA	130	Literature [4]. Repeat dose 0.5 – 10 mg / NCA	-	-	0.37%	AstraZeneca data on file.
	Mouse	42	AstraZeneca data on file / single s.c 10 nmol/kg / CMA	0.14	AstraZeneca data on file / single s.c 10 nmol/kg / CMA	2.3	AstraZeneca data on file / single s.c 10 nmol/kg / Calculated as $\ln(2)/(CL/F)*(Vd/F)$	-	-	-	-
	Rat	22	AstraZeneca data on file / single s.c and i.v. 50 - 400 µg/kg / CMA	0.15	AstraZeneca data on file / single s.c and i.v. 50 - 400 µg/kg / CMA	4.8	AstraZeneca data on file / single s.c and i.v. 50 - 400 µg/kg / CMA	38%	AstraZeneca data on file / single s.c and i.v. 50 - 400 µg/kg / CMA	-	-
	Minipig	19	AstraZeneca data on file / single s.c and i.v. 2.5 - 25 µg/kg / NCA	0.15	AstraZeneca data on file / single s.c and i.v. 2.5 - 25 µg/kg / NCA	5.7	AstraZeneca data on file / single s.c and i.v. 2.5 - 25 µg/kg / Calculated as $\ln(2)/(CL/F)*(Vd/F)$	90%	AstraZeneca data on file / single s.c and i.v. 2.5 - 25 µg/kg / NCA	-	-
	Monkey	17	AstraZeneca data on file / single s.c and i.v. 0.5 - 1 mg/kg / CMA	0.078	AstraZeneca data on file / single s.c and i.v. 0.5 - 1 mg/kg / CMA	3.1	AstraZeneca data on file / single s.c and i.v. 0.5 - 1 mg/kg / Calculated as $\ln(2)/(CL/F)*(Vd/F)$	94%	AstraZeneca data on file / single s.c and i.v. 0.5 - 1 mg/kg / CMA	-	-
Liraglutide	Human	11	Literature [5] / Multiple clinical trials 20 – 600 µg / CMA (population approach)	0.21	Literature [5] / Multiple clinical trials 20 – 600 µg / CMA (population approach)	13	Literature [5] / Multiple clinical trials 20 – 600 µg / CMA (population approach)	-	-	-	-
	Mouse	23	Regulatory documentation [6] / s.c. single 0.1 mg/kg / NCA (dose/AUC)	0.22	Regulatory documentation [6] / s.c. single 0.1 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	6.7	Regulatory documentation [6] / s.c. single 0.1 mg/kg / NCA	-	-	-	-
	Rat	31	Regulatory documentation [6] / s.c. single 0.1 mg/kg / NCA (dose/AUC)	0.15	Regulatory documentation [6] / s.c. single 0.1 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	3.5	Regulatory documentation [6] / s.c. single 0.1 mg/kg / NCA	-	-	-	-
	Monkey	27	Regulatory documentation [6] / s.c. single 0.05 mg/kg; i.v. 0.12 mg/kg / NCA (dose/AUC)	0.28	Regulatory documentation [6] / s.c. single 0.05 mg/kg; i.v. 0.12 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	7.1	Regulatory documentation [6] / s.c. single 0.05 mg/kg; i.v. 0.12 mg/kg / NCA	53%	Regulatory documentation [6] / s.c. single 0.05 mg/kg; i.v. 0.12 mg/kg / NCA	-	-
	Rabbit	19	Regulatory documentation [6] / s.c. single 0.01 mg/kg / NCA (dose/AUC)	0.19	Regulatory documentation [6] / s.c. single 0.01 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	7	Regulatory documentation [6] / s.c. single 0.01 mg/kg / NCA	-	-	-	-

Pemvidutide	Pig	18	Regulatory documentation [6] / s.c. single 0.002 mg/kg; i.v. 0.002 mg/kg / NCA (dose/AUC)	0.37	Regulatory documentation [6] / s.c. single 0.002 mg/kg; i.v. 0.002 mg/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	14	Regulatory documentation [6] / s.c. single 0.002 mg/kg; i.v. 0.002 mg/kg / NCA	76%	Regulatory documentation [6] / s.c. single 0.002 mg/kg; i.v. 0.002 mg/kg / NCA	-	-
	Minipig	5.8	Literature [2] / single s.c. 1.0 nmol/kg; single i.v. 0.5 nmol/kg / NCA	0.1	Literature [2] / single s.c. 1.0 nmol/kg; single i.v. 0.5 nmol/kg / NCA	12	Literature [2] / single s.c. 1.0 nmol/kg; single i.v. 0.5 nmol/kg / NCA	66%	Literature [2] / single s.c. 1.0 nmol/kg; single i.v. 0.5 nmol/kg / NCA	-	-
	Human	11	Literature [7] / single s.c. 5.0 µg/kg; single i.v. 5.0 µg/kg / NCA ($\text{CL}_{i.v}/F_{s.c.}$)	0.13	Literature [7] / single s.c. 5.0 µg/kg; single i.v. 5.0 µg/kg / NCA ($V_{d,i.v}/F_{s.c.}$)	8.1	Literature [7] / single s.c. 5.0 µg/kg; single i.v. 5.0 µg/kg / NCA	55%	Literature [7] / single s.c. 5.0 µg/kg; single i.v. 5.0 µg/kg / NCA	0.51%	Literature [8]
	Mouse	14	Literature [9] / s.c. single 10 nmol/kg / NCA (dose/AUC)	0.31	Literature [9] / s.c. single 10 nmol/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	15	Literature [9] / s.c. single 10 nmol/kg / NCA	-	-	-	-
	Rat	16	Literature [10] / s.c. single 10 nmol/kg / NCA (dose/AUC)	0.24	Literature [10] / s.c. single 10 nmol/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	10	Literature [10] / s.c. single 10 nmol/kg / NCA	-	-	-	-
	Mini-swine	0.93	Literature [10] / single s.c. 20 nmol /kg; single i.v. 20 nmol/kg / NCA (dose/AUC)	0.07	Literature [10] / single s.c. 20 nmol /kg; single i.v. 20 nmol/kg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	52	Literature [10] / single s.c. 20 nmol /kg; single i.v. 20 nmol/kg / NCA	73%	Literature [10] / single s.c. 20 nmol /kg; single i.v. 20 nmol/kg / NCA	-	-
Teduglutide	Human	1.4	Presentation [11] / s.c. 1.8 mg / NCA (dose/AUC)	0.22	Presentation [11] / s.c. 1.8 mg / NCA ($t_{1/2}/\ln(2)*\text{dose}/\text{AUC}$)	110	Presentation [11] / s.c. 1.8 mg / NCA	-	-	-	-
	Rat	860	Literature [12] / single s.c. 1-5 mg/kg; single i.v. 0.2 mg/kg / NCA ($\text{CL}_{i.v}/F_{s.c.}$)	0.13	Literature [12] / single s.c. 1-5 mg/kg; single i.v. 0.2 mg/kg / NCA ($V_{d,i.v}/F_{s.c.}$)	0.11	Literature [12] / single i.v. 0.2 mg/kg / NCA	69%	Literature [12] / single i.v. 0.2 mg/kg / NCA	100.00%	Assumed (naked peptide)
	Minipig	110	Literature [12] / single s.c. 0.15 mg/kg; single i.v. 0.1 mg/kg / NCA ($\text{CL}_{i.v}/F_{s.c.}$)	0.066	Literature [12] / single s.c. 0.15 mg/kg; single i.v. 0.1 mg/kg / NCA ($V_{d,i.v}/F_{s.c.}$)	0.41	Literature [12]. / single i.v. 0.1 mg/kg / NCA	53%	Literature [12]. / single s.c. 0.15 mg/kg; single i.v. 0.1 mg/kg / NCA	100.00%	Assumed (naked peptide)
	Monkey	190	Literature [12] / single s.c. 0.25 mg/kg; single i.v. 0.1 mg/kg / NCA ($\text{CL}_{i.v}/F_{s.c.}$)	0.07	Literature [12] / single s.c. 0.25 mg/kg; single i.v. 0.1 mg/kg / NCA ($V_{d,i.v}/F_{s.c.}$)	0.26	Literature [12]. / single i.v. 0.1 mg/kg / NCA	77%	Literature [12]. / single s.c. 0.25 mg/kg; single i.v. 0.1 mg/kg / NCA	100.00%	Assumed (naked peptide)

Apraglutide	Human	220	Literature [13] / repeat 0.05 mg/kg / NCA	0.4	Literature [13] / 0.05 mg/kg / NCA	1.2	Literature [13] / 0.05 mg/kg / NCA	-	-	100.00%	Assumed (naked peptide)
	Rat	25	Literature [12] / single s.c. 1-5 mg/kg; single i.v. 0.2 mg/kg / NCA (CL _{i.v} /F _{s.c.})	0.13	Literature [12] / single s.c. 1-5 mg/kg; single i.v. 0.2 mg/kg / NCA (V _{d,i.v} /F _{s.c.})	0.11	Literature [12] / single i.v. 0.2 mg/kg / NCA	69%	Literature [12] / single i.v. 0.2 mg/kg / NCA	0.80%	Literature [14]
	Minipig	4.5	Literature [12] / single s.c. 0.15 mg/kg; single i.v. 0.025 mg/kg / NCA (CL _{i.v} /F _{s.c.})	0.065	Literature [12] / single s.c. 0.15 mg/kg; single i.v. 0.025 mg/kg / NCA (V _{d,i.v} /F _{s.c.})	10	Literature [12]. / single i.v. 0.025 mg/kg / NCA	43%	Literature [12]. / single s.c. 0.15 mg/kg; single i.v. 0.025 mg/kg / NCA	0.80%	Assumed same as in the rat
	Monkey	8.6	Literature [12] / single s.c. 0.25 mg/kg; single i.v. 0.1 mg/kg / NCA (CL _{i.v} /F _{s.c.})	0.081	Literature [12] / single s.c. 0.25 mg/kg; single i.v. 0.1 mg/kg / NCA (V _{d,i.v} /F _{s.c.})	6.5	Literature [12]. / single i.v. 0.1 mg/kg / NCA	32%	Literature [12]. / single s.c. 0.25 mg/kg; single i.v. 0.1 mg/kg / NCA	0.80%	Assumed same as in the rat
Pramlintide	Human	9.5	Literature [15] / repeat 5 mg QW / CMA (population)	0.45	Literature [15] / repeat 5 mg QW / CMA (population)	33	Literature [15] / repeat 5 mg QW / CMA (population)	-	-	0.80%	Assumed same as in the rat
	Mouse	4100	Regulatory documentation [16] / single s.c. 0.2-1.2 mg/kg / NCA (dose/AUC)	-	-	-	-	-	-	100.00%	Assumed (naked peptide)
	Rat	12000	Regulatory documentation [16] / repeat s.c. 0.04-0.6 mg/kg / NCA (dose/AUC)	-	-	-	-	-	-	100.00%	Assumed (naked peptide)
	Dog	3800	Regulatory documentation [16] / repeat s.c. 0.1-0.6 mg/kg / NCA (dose/AUC)	-	-	-	-	-	-	100.00%	Assumed (naked peptide)
	Rabbit	3200	Regulatory documentation [16] / single s.c. 0.03-0.3 mg/kg / NCA (dose/AUC)	-	-	-	-	-	-	100.00%	Assumed (naked peptide)
	Human	2000	Regulatory documentation [16] / 0.03-0.12 mg / NCA (dose/AUC)	-	-	-	-	-	-	100.00%	Assumed (naked peptide)

Exenatide	Rat	600	Literature [17] / single s.c. 0.5-50 nmol; i.v. 0.5-50 nmol / CMA (derived from model parameters)	0.28	Literature [17] / single s.c. 0.5-50 nmol; i.v. 0.5-50 nmol / CMA (derived from model parameters)	0.32	Literature [17] / single s.c. 0.5-50 nmol; i.v. 0.5-50 nmol / CMA (derived from model parameters)	100%	Literature [17] / single s.c. 0.5-50 nmol; i.v. 0.5-50 nmol / CMA	100.00%	Assumed (naked peptide)
	Monkey	210	Literature [17] / single s.c. 1-3 µg/kg; i.v. 3 µg/kg / CMA (derived from model parameters)	0.34	Literature [17] / single s.c. 1-3 µg/kg; i.v. 3 µg/kg / CMA (derived from model parameters)	1.1	Literature [17] / single s.c. 1-3 µg/kg; i.v. 3 µg/kg / CMA (derived from model parameters)	69%	Literature [17] / single s.c. 1-3 µg/kg; i.v. 3 µg/kg / CMA (derived from model parameters)	100.00%	Assumed (naked peptide)
	Human	87	Literature [17] / single s.c. 0.02-0.4 µg/kg; i.v. inf. 0.066 pmol/kg/min*360 min / CMA (derived from model parameters)	0.2	Literature [17] / single s.c. 0.02-0.4 µg/kg; i.v. inf. 0.066 pmol/kg/min*360 min / CMA (derived from model parameters)	1.6	Literature [17] / single s.c. 0.02-0.4 µg/kg; i.v. inf. 0.066 pmol/kg/min*360 min / CMA (derived from model parameters)	100%	Literature [17] / single s.c. 0.02-0.4 µg/kg; i.v. inf. 0.066 pmol/kg/min*360 min / CMA (derived from model parameters)	100.00%	Assumed (naked peptide)

Table S2. Peptide volume of distribution (V_d) range in plasma across species based on the Oie and Tozer model [18] applying physiological parameters from Davies and Morris [19]. V_E and V_p denote the extracellular volume outside the plasma volume and the plasma volume, respectively, whereas $R_{E/I}$ is the ratio of the total number of binding sites or the amount of protein in V_E to that in plasma. f_u denotes the fraction unbound in plasma.

	<i>BW (kg)</i>	<i>Extracellular volume (L/kg)¹</i>	<i>V_p (L/kg)¹</i>	<i>V_E (L/kg)¹</i>	<i>R_{E/I}</i>	<i>V_p × (1+R_{E/I}) (L/kg)</i>	<i>V_p × (V_{IF}/V_p - R_{E/I}) (L/kg)</i>	<i>V_d (L/kg)</i>	<i>V_d range (L/kg)</i>
Mouse	0.020	0.30 (41%)	0.05 (6.9%)	0.25 (34%)	1.4	0.12	0.18	$0.12 + f_u \times 0.18$	0.12 - 0.30
Rat	0.25	0.30 (44%)	0.031 (4.7%)	0.27 (40%)	1.4	0.075	0.22	$0.075 + f_u \times 0.22$	0.075 - 0.30
Monkey	5.0	0.21 (30%)	0.045 (6.5%)	0.16 (24%)	1.4	0.11	0.10	$0.11 + f_u \times 0.10$	0.11 - 0.21
Dog	10	0.28 (46%)	0.052 (8.5%)	0.22 (37%)	1.4	0.12	0.15	$0.12 + f_u \times 0.15$	0.12 - 0.28
Human	70	0.26 (43%)	0.043 (7.1%)	0.22 (36%)	1.4	0.10	0.16	$0.10 + f_u \times 0.16$	0.10 - 0.26

¹ fraction of total body water in parentheses.

Table S3. Clearance scaling across species: estimated allometric exponents for clearance following subcutaneous administration (CL/F). The geometric mean for evaluated peptides is 0.72.

<i>Peptide</i>	<i>Number of species</i>	<i>Allometric exponent¹</i>	<i>R²</i>
<i>Pramlintide</i>	5	0.88 (0.72 – 1.0)	0.95
<i>Teduglutide</i>	4	0.72 (0.51 - 0.92)	0.93
<i>Exenatide</i>	3	0.66 (0.64 - 0.67)	1.0
<i>Cotadutide</i>	5	0.87 (0.81 - 0.92)	0.99
<i>Liraglutide</i>	7	0.88 (0.77 - 0.98)	0.96
<i>Apraglutide</i>	4	0.77 (0.59 - 0.95)	0.96
<i>Pemvidutide</i>	4	0.65 (0.50 - 0.80)	0.96
<i>Tirzepatide</i>	3	0.60 (0.45 - 0.76)	0.99
<i>Semaglutide</i>	5	0.58 (0.49 - 0.67)	0.96

¹ Range indicate 80% confidence interval.

Table S4. Volume of distribution scaling across species: estimated allometric exponents for volume following subcutaneous administration (V_d/F).

The geometric mean for evaluated peptides is 0.98.

<i>Peptide</i>	<i>Number of species</i>	<i>Allometric exponent¹</i>	<i>R²</i>
<i>Teduglutide</i>	4	1.1 (0.65 - 1.5)	0.88
<i>Exenatide</i>	3	0.94 (0.70 - 1.2)	0.99
<i>Cotadutide</i>	5	1.0 (0.92 - 1.1)	0.99
<i>Liraglutide</i>	7	0.98 (0.87 - 1.1)	0.97
<i>Apraglutide</i>	4	1.1 (0.7 - 1.5)	0.89
<i>Pemvidutide</i>	4	0.89 (0.74 - 1.0)	0.98
<i>Tirzepatide</i>	3	0.92 (0.79 - 1.0)	1.0
<i>Semaglutide</i>	5	0.93 (0.90 - 0.96)	1.0

¹ Range indicate 80% confidence interval.

Table S5. Half-life scaling across species: estimated allometric exponents for half-life. The geometric mean for evaluated peptides is 0.25.

<i>Peptide</i>	<i>Number of species</i>	<i>Allometric exponent¹</i>	<i>R²</i>
<i>Teduglutide</i>	4	0.34 (0.11 - 0.57)	0.70
<i>Exenatide</i>	3	0.29 (0.031 - 0.55)	0.84
<i>Cotadutide</i>	5	0.15 (0.037 - 0.27)	0.48
<i>Liraglutide</i>	7	0.10 (0.021 - 0.18)	0.29
<i>Apraglutide</i>	4	0.34 (0.10 - 0.58)	0.68
<i>Pemvidutide</i>	4	0.24 (0.068 - 0.41)	0.67
<i>Tirzepatide</i>	3	0.31 (0.028 - 0.60)	0.84
<i>Semaglutide</i>	5	0.35 (0.24 - 0.46)	0.87

¹ Range indicate 80% confidence interval.

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