Electronic supplementary material

Clinical Pharmacokinetics

Pharmacokinetic and pharmacodynamic properties of faster-acting insulin aspart versus insulin aspart across a clinically relevant dose range in subjects with type 1 diabetes mellitus

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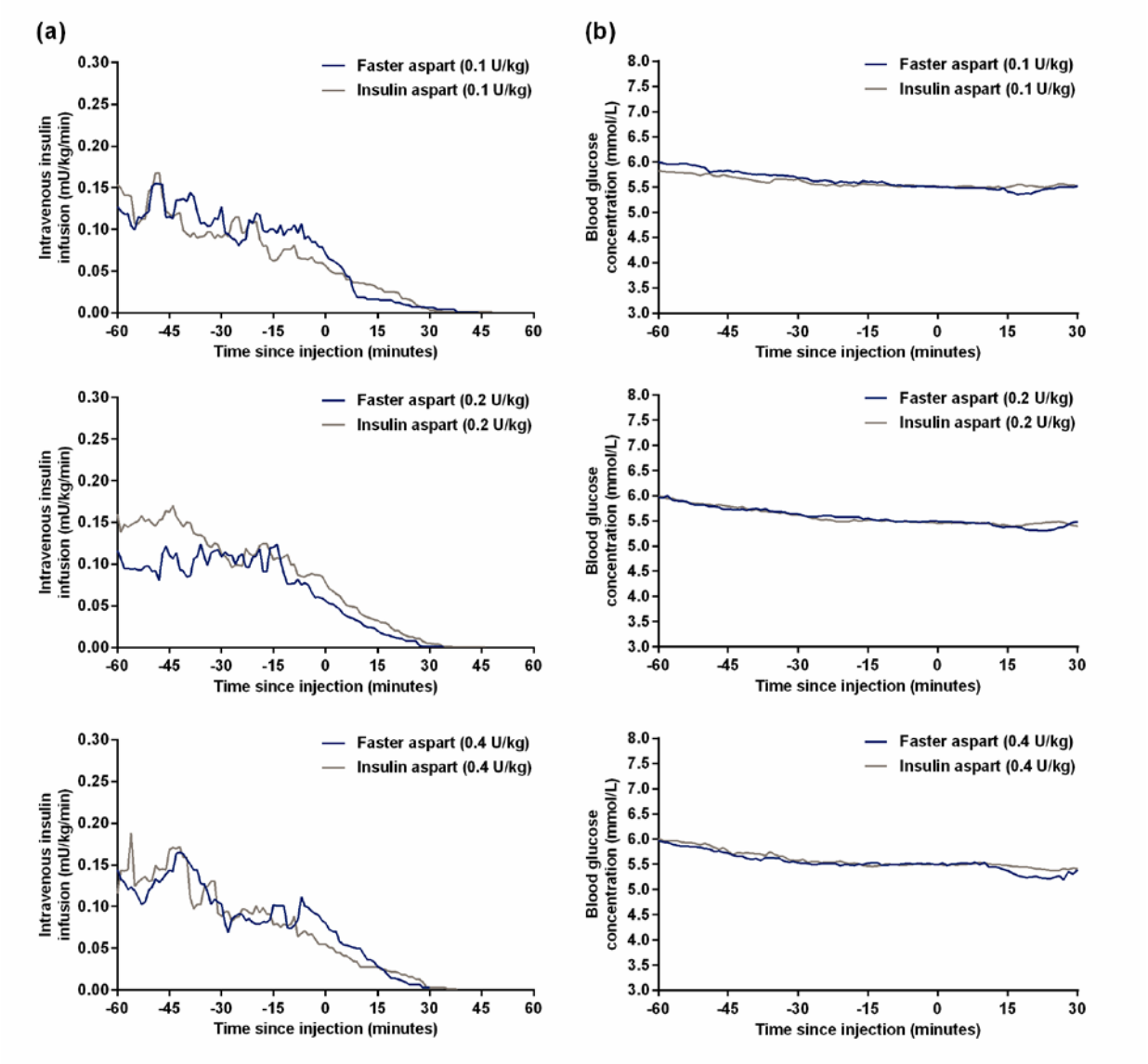


Fig. S1 Mean intravenous insulin infusion from -60 min until blood glucose had fallen by 0.3 mmol/L (5 mg/dL) after dosing (a) and blood glucose concentration from -60 min until 30 min (b) for faster aspart versus insulin aspart at three different dose levels

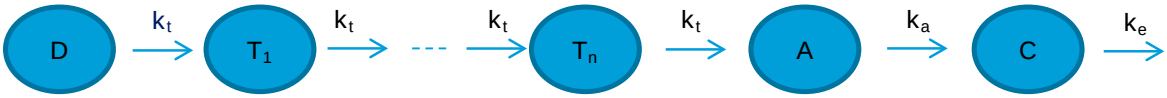
Table S1 Clamp quality for faster aspart and insulin aspart

	Faster aspart[a] Mean±SD	Insulin aspart[a] Mean±SD
Precision[b] (%)		
0.1 U/kg	4.8±3.9	4.7±3.1
0.2 U/kg	4.8±2.2	5.1±2.2
0.4 U/kg	5.1±2.0	5.6±3.8
Control deviation[c] (mg/dL)		
0.1 U/kg	0.4±1.7	0.8±1.8
0.2 U/kg	-0.2±0.9	-0.5±1.5
0.4 U/kg	-0.7±1.4	-1.1±1.9

[a] Data are calculated between the timepoints $t_{10\%\ AUCGIR,0\text{-}t}$ and $t_{90\%\ AUCGIR,0\text{-}t}$ to exclude intentional blood glucose deviations from target in the beginning and end of the clamp (in the beginning of the clamp, the clamp design to determine onset of action implied blood glucose deviations from target, while in the end of the clamp, escape of blood glucose from target occurs due to a decreasing insulin action).
[b] The coefficient of variation of the ClampArt blood glucose measurements.
[c] The mean difference between the ClampArt blood glucose measurements and the target blood glucose level.
AUC, area under the curve; GIR, glucose infusion rate; SD, standard deviation; t, time of last GIR observation > 0; $t_{10\%\ AUCGIR,0\text{-}t}$, time to 10% of $AUC_{GIR,0\text{-}t}$; $t_{90\%\ AUCGIR,0\text{-}t}$, time to 90% of $AUC_{GIR,0\text{-}t}$.

Compartmental modelling

The compartmental model used to calculate onset of appearance and AUC_{IAsp} endpoints was a transit compartment model consisting of a dosing compartment, 3 transit compartments, an absorption compartment and a central compartment. The model is illustrated below for n transit compartments (D, T_i, A and C are drug amounts in the dose compartment, the i^{th} transit compartment, the absorption compartment and the central compartment, respectively).



The model was fitted to individual serum insulin aspart concentrations for each pharmacokinetic time profile. The procedure PROC NLMIXED (without random effects) in SAS (version 9.3; SAS Institute, Cary, NC, USA) was used with serum insulin aspart concentration as response and actual time as covariate, assuming an additive error on log scale. The lower limit of quantification (LLOQ) was 10 pmol/L and the values below LLOQ were treated as censored (i.e. between 0 and 10 pmol/L). The model parameters were fractional transit rate (k_t), fractional absorption rate (k_a), fractional elimination rate (k_e) and apparent volume of distribution of the central compartment (V). All parameters were estimated on log scale and it was assumed that k_a was greater than k_e. The latter was ensured by using the parameterisation $k_a=k_e+k_d$, $k_d>0$. In case convergence was not reached or the standard error of $\log(k_d)$ was not able to estimate or greater than 5, the model was re-run assuming $k_a=k_e$. The compartmental modelling approach was specified prior to database lock.

Table S2 Pharmacokinetic results for faster aspart and insulin aspart in subjects with type 1 diabetes mellitus

	Faster aspart[a]	Insulin aspart[a]	Treatment ratio[b] [95% CI]	Treatment difference[c] [95% CI]	P-value
Onset of exposure					
Onset of appearance (min)					
0.1 U/kg	5.3	10.0	0.53 [0.42;0.64]	-4.7 [-6.0;-3.4]	<0.001
0.2 U/kg	4.0	8.8	0.46 [0.38;0.54]	-4.7 [-5.4;-4.0]	<0.001
0.4 U/kg	3.2	7.3	0.44 [0.31;0.57]	-4.1 [-5.3;-3.0]	<0.001
$t_{Early\ 50\%\ Cmax}$ (min)					
0.1 U/kg	20.3	29.9	0.68 [0.59;0.78]	-9.6 [-12.9;-6.3]	<0.001
0.2 U/kg	24.2	32.0	0.76 [0.71;0.81]	-7.8 [-9.6;-6.0]	<0.001
0.4 U/kg	24.6	36.1	0.68 [0.60;0.76]	-11.5 [-14.9;-8.1]	<0.001
t_{max} (min)					
0.1 U/kg	57.0	65.7	0.87 [0.76;0.98]	-8.7 [-16.6;-0.8]	0.031
0.2 U/kg	65.2	72.1	0.90 [0.82;1.00]	-6.9 [-13.6;-0.3]	0.042
0.4 U/kg	72.1	75.2	0.96 [0.83;1.10]	-3.1 [-13.4; 7.2]	0.546
Early exposure					
$AUC_{IAsp,0\text{-}15min}$ (pmol·h/L)					
0.1 U/kg	6.4	2.2	2.85 [2.21;3.67]		<0.001
0.2 U/kg	12.0	3.0	3.95 [3.27;4.78]		<0.001
0.4 U/kg	22.9	5.4	4.20 [3.26;5.42]		<0.001
$AUC_{IAsp,0\text{-}30min}$ (pmol·h/L)					
0.1 U/kg	26.8	17.4	1.54 [1.29;1.83]		<0.001
0.2 U/kg	53.7	25.7	2.09 [1.83;2.38]		<0.001
0.4 U/kg	108.7	49.4	2.20 [1.85;2.62]		<0.001
$AUC_{IAsp,0\text{-}1h}$ (pmol·h/L)					
0.1 U/kg	84.6	77.3	1.09 [0.97;1.24]		0.143
0.2 U/kg	184.6	133.6	1.38 [1.26;1.51]		<0.001
0.4 U/kg	385.5	286.4	1.35 [1.19;1.52]		<0.001
$AUC_{IAsp,0\text{-}1.5h}$ (pmol·h/L)					
0.1 U/kg	139.4	140.6	0.99 [0.89;1.10]		0.869
0.2 U/kg	314.7	259.1	1.21 [1.12;1.31]		<0.001
0.4 U/kg	670.4	581.0	1.15 [1.04;1.28]		0.007
$AUC_{IAsp,0\text{-}2h}$ (pmol·h/L)					
0.1 U/kg	183.2	191.5	0.96 [0.87;1.05]		0.364
0.2 U/kg	423.2	368.8	1.15 [1.07;1.23]		<0.001
0.4 U/kg	912.6	848.9	1.08 [0.98;1.18]		0.139

	Faster aspart[a]	Insulin aspart[a]	Treatment ratio[b] [95% CI]	Treatment difference[c] [95% CI]	P-value
Overall exposure					
$AUC_{IAsp,0-t}$ (pmol·h/L)					
0.1 U/kg	303.1	330.4	0.92 [0.85;0.99]		0.021
0.2 U/kg	727.4	703.8	1.03 [0.98;1.09]		0.237
0.4 U/kg	1614.6	1737.1	0.93 [0.86;1.00]		0.050
C_{max} (pmol/L)					
0.1 U/kg	133.9	154.9	0.86 [0.78;0.96]		0.009
0.2 U/kg	323.1	287.3	1.12 [1.04;1.22]		0.005
0.4 U/kg	683.3	691.4	0.99 [0.89;1.10]		0.830

[a] Data are least square means.
[b] Faster aspart/insulin aspart (for onset of exposure endpoints, the treatment ratio was calculated using Fieller's method).
[c] Faster aspart - insulin aspart.
AUC, area under the curve; CI, confidence interval; C_{max}, maximum insulin aspart concentration; IAsp, insulin aspart; $t_{Early\ 50\%\ Cmax}$, time to 50% of maximum insulin aspart concentration in the early part of the pharmacokinetic profile; t_{max}, time to maximum insulin aspart concentration.

Table S3 Pharmacodynamic results for faster aspart and insulin aspart in subjects with type 1 diabetes mellitus

	Faster aspart[a]	Insulin aspart[a]	Treatment ratio[b] [95% CI]	Treatment difference[c] [95% CI]	P-value
Onset of glucose-lowering effect					
Onset of action (min)					
0.1 U/kg	19.8	24.8	0.80 [0.63;1.00]	-5.0 [-10.0;-0.0]	0.049
0.2 U/kg	16.9	22.8	0.74 [0.64;0.86]	-5.8 [-8.6;-3.1]	<0.001
0.4 U/kg	16.1	21.7	0.74 [0.62;0.88]	-5.6 [-8.8;-2.4]	<0.001
$t_{Early\ 50\%\ GIRmax}$ (min)					
0.1 U/kg	29.6	38.4	0.77 [0.68;0.88]	-8.8 [-13.0;-4.5]	<0.001
0.2 U/kg	36.3	46.6	0.78 [0.70;0.86]	-10.2 [-14.3;-6.2]	<0.001
0.4 U/kg	35.4	47.2	0.75 [0.69;0.82]	-11.8 [-15.3;-8.3]	<0.001
$tGIR_{max}$ (min)					
0.1 U/kg	90.6	116.6	0.78 [0.62;0.96]	-26.0 [-48.3;-3.6]	0.024
0.2 U/kg	121.9	131.9	0.92 [0.86;0.99]	-10.0 [-18.3;-1.7]	0.019
0.4 U/kg	133.0	162.7	0.82 [0.74;0.91]	-29.7 [-45.1;-14.4]	<0.001
Early glucose-lowering effect					
$AUC_{GIR,0-30min}$ (mg/kg)					
0.1 U/kg	35.0	23.6	1.48 [1.00;2.41]		0.054
0.2 U/kg	50.6	26.4	1.92 [1.51;2.58]		<0.001
0.4 U/kg	65.7	30.9	2.13 [1.60;3.06]		<0.001
$AUC_{GIR,0-1h}$ (mg/kg)					
0.1 U/kg	138.0	110.6	1.25 [1.06;1.49]		0.009
0.2 U/kg	192.0	150.0	1.28 [1.17;1.41]		<0.001
0.4 U/kg	270.0	194.2	1.39 [1.24;1.57]		<0.001
$AUC_{GIR,0-1.5h}$ (mg/kg)					
0.1 U/kg	233.0	205.7	1.13 [1.02;1.26]		0.023
0.2 U/kg	355.5	303.8	1.17 [1.08;1.27]		<0.001
0.4 U/kg	518.6	411.0	1.26 [1.13;1.40]		<0.001
$AUC_{GIR,0-2h}$ (mg/kg)					
0.1 U/kg	347.3	315.7	1.10 [0.99;1.22]		0.073
0.2 U/kg	558.6	503.2	1.11 [1.03;1.20]		0.009
0.4 U/kg	798.7	675.6	1.18 [1.07;1.31]		0.002

	Faster aspart[a]	Insulin aspart[a]	Treatment ratio[b] [95% CI]	Treatment difference[c] [95% CI]	P-value
Overall glucose-lowering effect					
$AUC_{GIR,0-t}$ (mg/kg)					
0.1 U/kg	646.8	656.1	0.99 [0.89;1.09]		0.773
0.2 U/kg	1352.8	1391.1	0.97 [0.90;1.05]		0.451
0.4 U/kg	2338.7	2410.2	0.97 [0.88;1.07]		0.544
GIR_{max} (mg/kg/min)					
0.1 U/kg	4.2	4.2	1.00 [0.91;1.10]		0.920
0.2 U/kg	7.1	7.3	0.98 [0.91;1.05]		0.550
0.4 U/kg	10.0	10.0	1.00 [0.91;1.10]		0.999

[a] Data are least square means.
[b] Faster aspart/insulin aspart (for onset of effect endpoints as well as for $AUC_{GIR,0-30min}$ and $AUC_{GIR,0-1h}$, the treatment ratio was calculated using Fieller's method)
[c] Faster aspart - insulin aspart
AUC, area under the curve; CI, confidence interval; GIR, glucose infusion rate; GIR_{max}, maximum glucose infusion rate; t, time of last GIR observation > 0; $t_{Early\ 50\%\ GIRmax}$, time to 50% of maximum glucose infusion rate in the early part of the glucose infusion rate profile; $tGIR_{max}$, time to maximum glucose infusion rate.

Table S4 Between-subject variability in glucose-lowering effect for faster aspart versus insulin aspart

	Faster aspart	Insulin aspart	P-value
	Coefficient of variation (%)		
Early glucose-lowering effect			
$AUC_{GIR,0\text{-}1h}$	35.1	37.1	0.837
$AUC_{GIR,0\text{-}2h}$	37.4	28.2	0.290
Overall glucose-lowering effect			
$AUC_{GIR,0\text{-}t}$	22.1	18.9	0.591
GIR_{max}	29.9	18.0	0.130

Coefficient of variation data are model-based estimates.
AUC, area under the curve; GIR, glucose infusion rate; GIR_{max}, maximum glucose infusion rate; t, time of last GIR observation > 0.

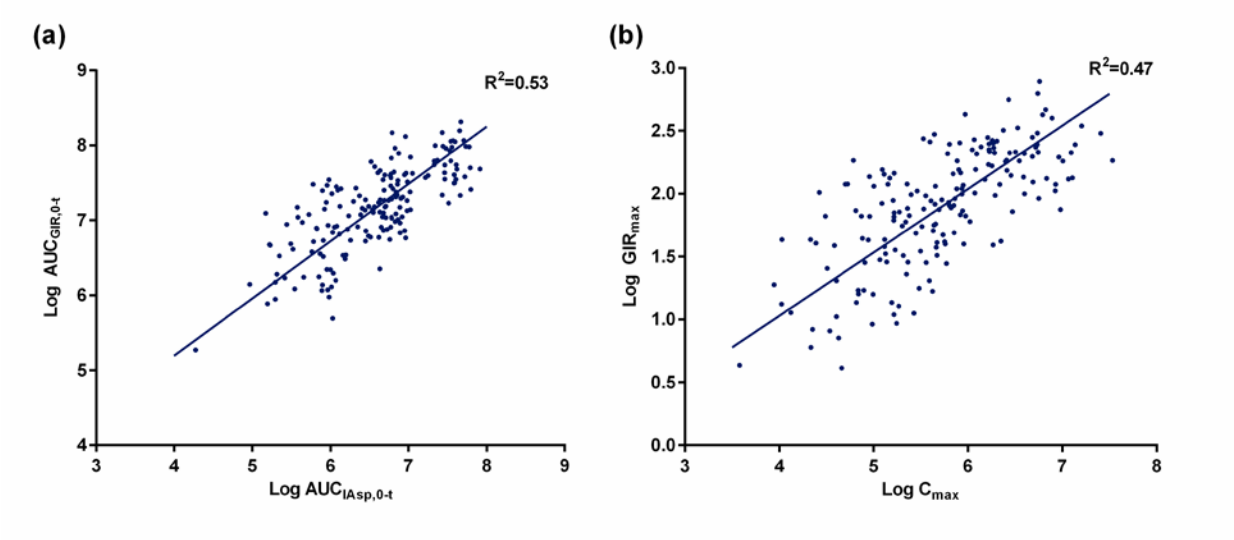


Fig. S2 Relationship between total exposure ($AUC_{IAsp,0\text{-}t}$) and total glucose-lowering effect ($AUC_{GIR,0\text{-}t}$) (a) and between maximum concentration (C_{max}) and maximum glucose-lowering effect (GIR_{max}) (b) for faster aspart, including the estimated regression line and the coefficient of determination (R^2).