フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.2.5. 付録

3. 臨床薬理試験の結果に基づく図表

ノボ ノルディスク ファーマ株式会社

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1: Pooled PK data - baseline characteristics - adults Trials 3887, 3888 (adults), 3889, 3891 (younger adults), 3921 and 3978 (FIA(Q) and NovoRapid)

Trial	Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
Pooled	Both	Age (years)	218	18	25	34	36	46	63
		Weight (kg)	218	52.6	67.1	75.3	75.6	83.5	105.7
		BMI	218	18.9	22.5	24.1	24.1	26.0	28.7
		Total insulin aspart antibodies (% B/T)	218	-0.12	3.62	9.61	14.77	20.37	76.88
	Male	Age (years)	153	18	26	34	37	46	60
		Weight (kg)	153	53.5	73.1	79.0	79.8	87.9	105.7
		BMI	153	18.9	23.2	24.5	24.5	26.3	28.7
		Total insulin aspart antibodies (% B/T)	153	-0.12	3.86	10.25	16.01	23.82	76.88
	Female	Age (years)	65	18	24	33	35	45	63
		Weight (kg)	65	52.6	59.7	65.7	65.8	71.6	85.5
		BMI	65	19.3	21.5	22.8	23.2	24.9	28.0
		Total insulin aspart antibodies (% B/T)	65	0.16	3.14	9.49	11.84	17.91	48.85
NN1218-3887	Both	Age (years)	46	20	37	44	44	54	61
		Weight (kg)	46	52.6	70.0	77.1	77.4	85.4	95.3
		BMI	46	19.3	23.5	24.7	24.6	26.5	28.2
		Total insulin aspart antibodies (% B/T)	46	0.16	2.73	11.33	15.44	24.03	65.74
	Male	Age (years)	35	21	37	44	44	54	59
		Weight (kg)	35	61.0	74.2	80.8	81.0	90.4	95.3
		BMI	35	20.0	23.8	25.1	25.2	26.9	28.2
		Total insulin aspart antibodies (% B/T)	35	0.16	3.07	11.41	16.80	25.79	65.74
	Female	Age (years)	11	20	37	44	44	55	61
		Weight (kg)	11	52.6	59.9	67.2	66.1	73.4	78.2

Pooled PK data - baseline characteristics - adults
Trials 3887, 3888 (adults), 3889, 3891 (younger adults), 3921 and 3978 (FIA(Q) and NovoRapid)

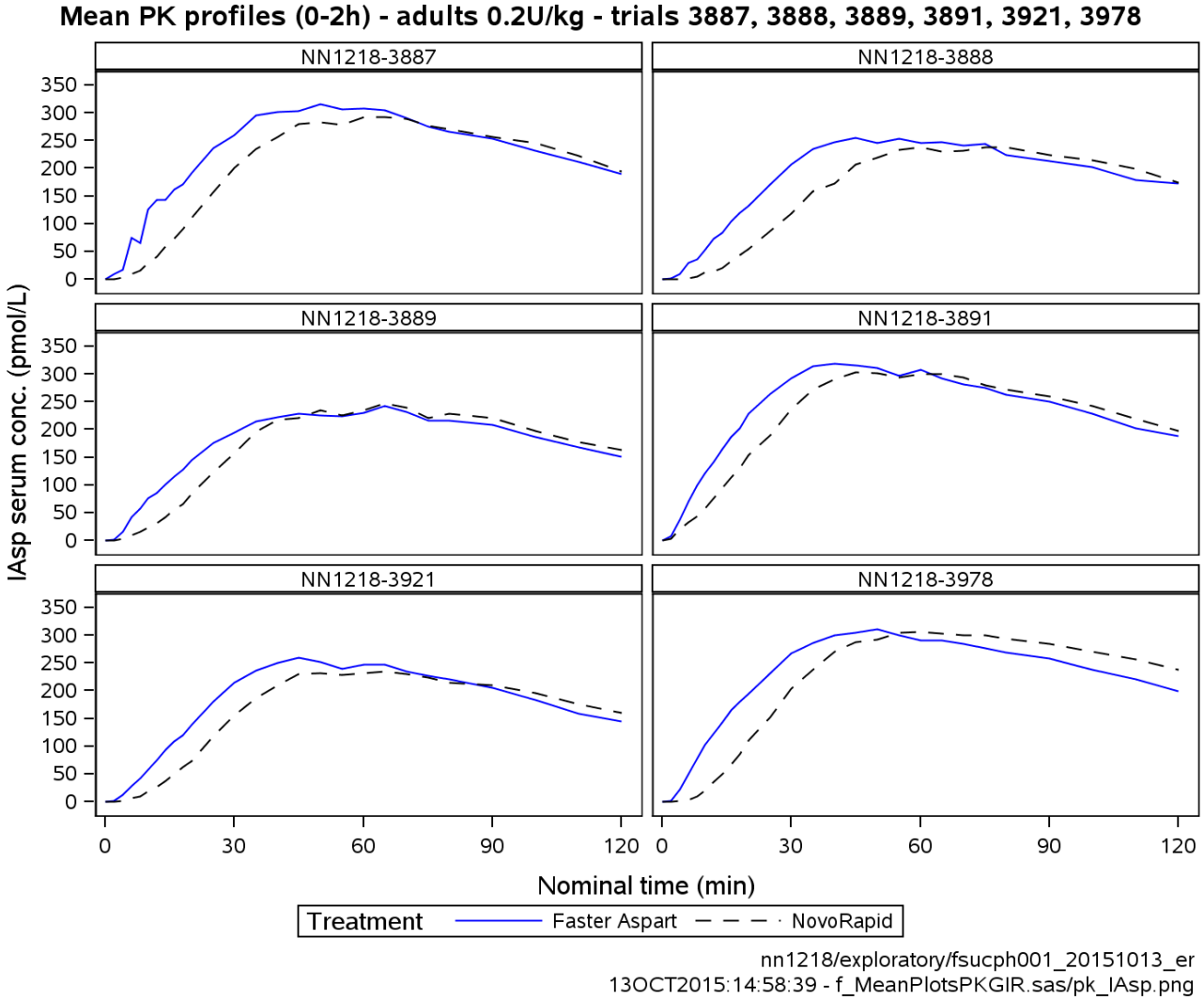
Trial	Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
NN1218-3887	Female	BMI	11	19.3	20.5	22.1	22.7	25.3	28.0
		Total insulin aspart antibodies (% B/T)	11	0.16	0.54	10.80	11.11	21.01	29.78
NN1218-3888	Both	Age (years)	15	18	19	19	20	21	25
		Weight (kg)	15	54.4	67.9	74.6	77.6	87.9	105.7
		BMI	15	20.5	21.1	22.9	23.8	27.5	27.9
		Total insulin aspart antibodies (% B/T)	15	0.67	3.62	11.97	18.68	40.38	58.61
	Male	Age (years)	11	18	19	19	20	21	25
		Weight (kg)	11	67.9	72.3	78.2	81.4	88.3	105.7
		BMI	11	20.5	21.1	22.9	23.8	27.5	27.9
		Total insulin aspart antibodies (% B/T)	11	2.47	3.62	13.26	23.28	45.13	58.61
	Female	Age (years)	4	18	19	21	21	24	24
		Weight (kg)	4	54.4	59.1	64.9	67.4	75.8	85.5
		BMI	4	20.7	21.4	22.7	23.5	25.7	27.9
		Total insulin aspart antibodies (% B/T)	4	0.67	2.37	5.25	6.03	9.69	12.94
NN1218-3889	Both	Age (years)	36	22	27	38	37	46	54
		Weight (kg)	36	52.9	64.6	70.2	72.8	81.7	96.2
		BMI	36	19.3	22.2	22.9	23.5	24.9	27.8
		Total insulin aspart antibodies (% B/T)	36	-0.12	4.16	11.13	17.81	27.93	76.88
	Male	Age (years)	21	22	26	38	37	45	54
		Weight (kg)	21	60.3	73.5	77.1	79.3	88.0	96.2
		BMI	21	19.7	22.5	24.3	24.2	25.7	27.8

Pooled PK data - baseline characteristics - adults
Trials 3887, 3888 (adults), 3889, 3891 (younger adults), 3921 and 3978 (FIA(Q) and NovoRapid)

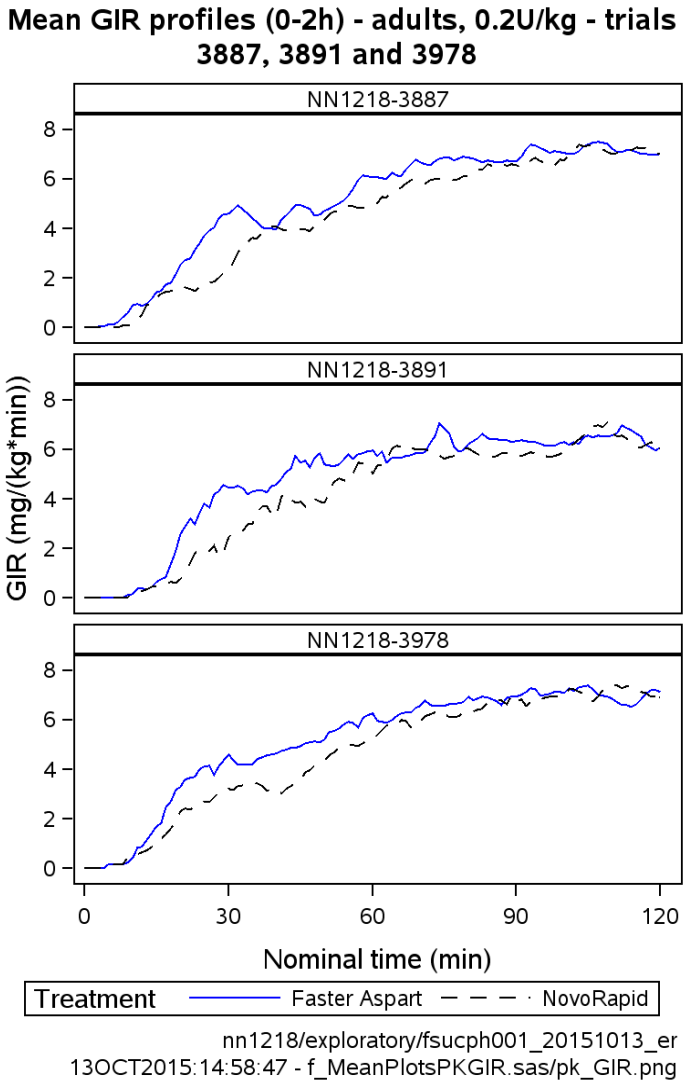
Trial	Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
NN1218-3889	Male	Total insulin aspart antibodies (% B/T)	21	-0.12	4.04	12.80	19.33	27.97	76.88
	Female	Age (years)	15	22	29	39	38	46	54
		Weight (kg)	15	52.9	60.0	63.7	63.7	66.6	77.1
		BMI	15	19.3	21.7	22.4	22.6	23.0	26.4
		Total insulin aspart antibodies (% B/T)	15	1.39	4.22	9.72	15.68	18.90	48.85
NN1218-3891	Both	Age (years)	37	22	24	26	27	31	34
		Weight (kg)	37	56.8	69.3	74.6	76.5	82.6	98.0
		BMI	37	20.7	23.4	24.8	24.7	26.5	27.9
		Total insulin aspart antibodies (% B/T)	37	0.33	3.81	9.49	12.90	19.44	46.50
	Male	Age (years)	23	22	24	26	27	31	34
		Weight (kg)	23	65.6	72.9	77.9	80.3	87.8	98.0
		BMI	23	20.7	22.9	24.3	24.6	26.5	27.9
		Total insulin aspart antibodies (% B/T)	23	1.40	3.95	8.59	14.95	27.02	46.50
	Female	Age (years)	14	22	23	27	27	30	34
		Weight (kg)	14	56.8	63.0	71.3	70.3	80.0	82.1
		BMI	14	20.9	23.4	25.2	24.9	26.9	27.8
		Total insulin aspart antibodies (% B/T)	14	0.33	2.03	10.47	9.52	14.32	24.27
NN1218-3921	Both	Age (years)	33	19	25	34	35	43	63
		Weight (kg)	33	53.3	62.6	72.0	73.0	82.5	95.4
		BMI	33	19.6	22.0	23.4	23.6	24.6	28.2
		Total insulin aspart antibodies (% B/T)	33	0.58	3.49	8.34	13.75	18.87	56.64

Pooled PK data - baseline characteristics - adults
Trials 3887, 3888 (adults), 3889, 3891 (younger adults), 3921 and 3978 (FIA(Q) and NovoRapid)

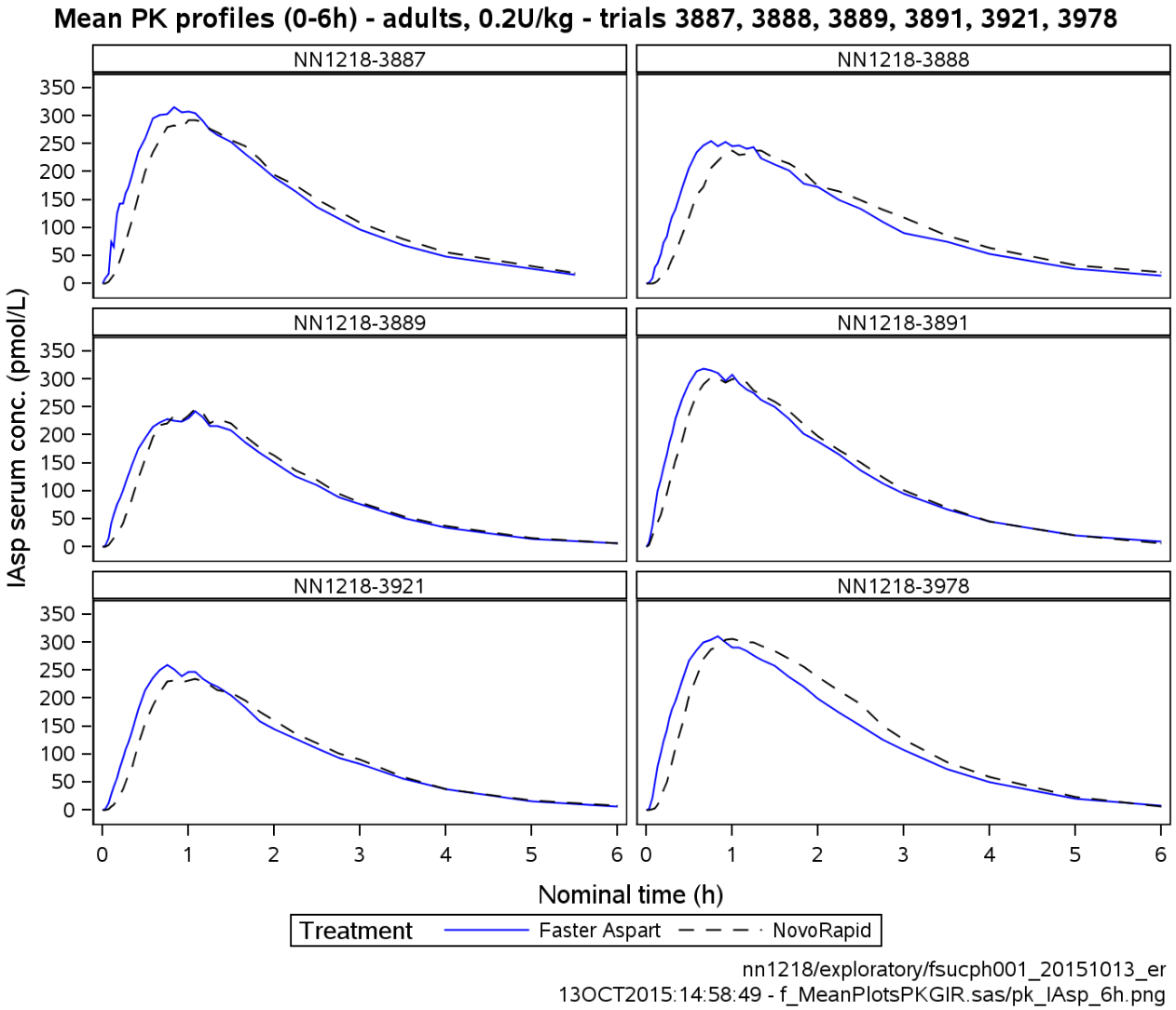
Trial	Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
NN1218-3921	Male	Age (years)	21	19	27	34	34	39	56
		Weight (kg)	21	62.6	72.0	80.5	80.0	89.2	95.4
		BMI	21	20.3	23.4	24.3	24.2	24.7	28.2
		Total insulin aspart antibodies (% B/T)	21	0.58	5.53	10.92	16.19	21.58	56.64
	Female	Age (years)	12	20	23	33	36	47	63
		Weight (kg)	12	53.3	56.2	58.4	60.9	65.6	75.9
		BMI	12	19.6	21.0	21.8	22.5	23.0	27.9
		Total insulin aspart antibodies (% B/T)	12	0.93	3.24	4.05	9.50	15.67	35.83
NN1218-3978	Both	Age (years)	51	21	28	42	40	48	60
		Weight (kg)	51	53.3	71.2	76.5	76.4	83.2	96.9
		BMI	51	18.9	22.8	24.3	24.3	26.0	28.7
		Total insulin aspart antibodies (% B/T)	51	0.47	4.58	8.46	12.89	19.22	66.94
	Male	Age (years)	42	21	30	43	40	49	60
		Weight (kg)	42	53.5	72.6	78.7	78.3	83.9	96.9
		BMI	42	18.9	23.0	24.4	24.5	26.3	28.7
		Total insulin aspart antibodies (% B/T)	42	0.47	3.86	7.99	12.29	15.95	66.94
	Female	Age (years)	9	23	27	41	37	47	51
		Weight (kg)	9	53.3	60.8	70.5	67.5	73.8	77.5
		BMI	9	19.7	21.0	24.2	23.1	24.6	25.4
		Total insulin aspart antibodies (% B/T)	9	1.53	5.08	19.19	15.66	20.37	37.31



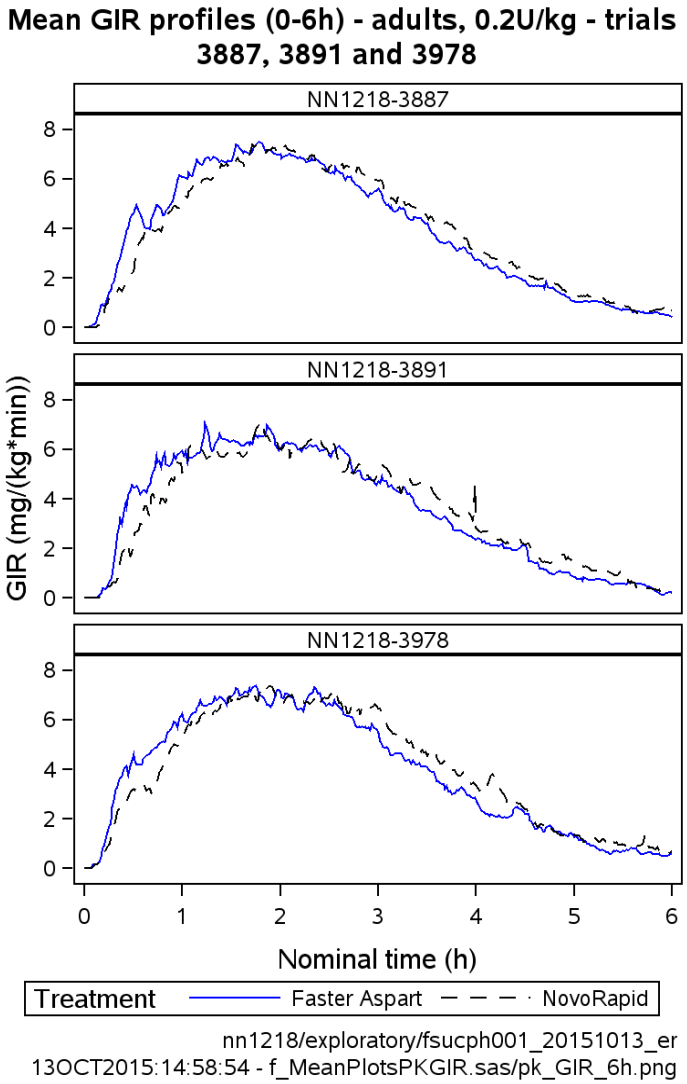
2: Mean PK profiles (0-2h) - adults 0.2U/kg - trials 3887, 3888, 3889, 3891, 3921, 3978



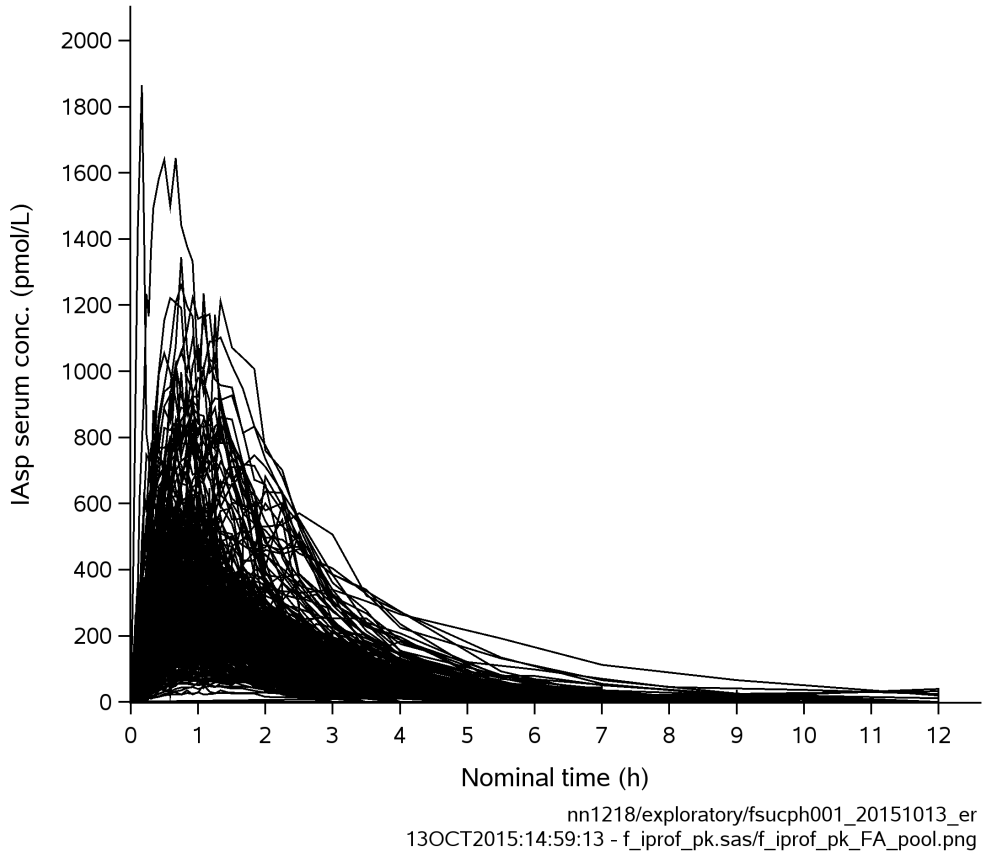
3: Mean GIR profiles (0-2h) - adults, 0.2U/kg - trials 3887, 3891 and 3978



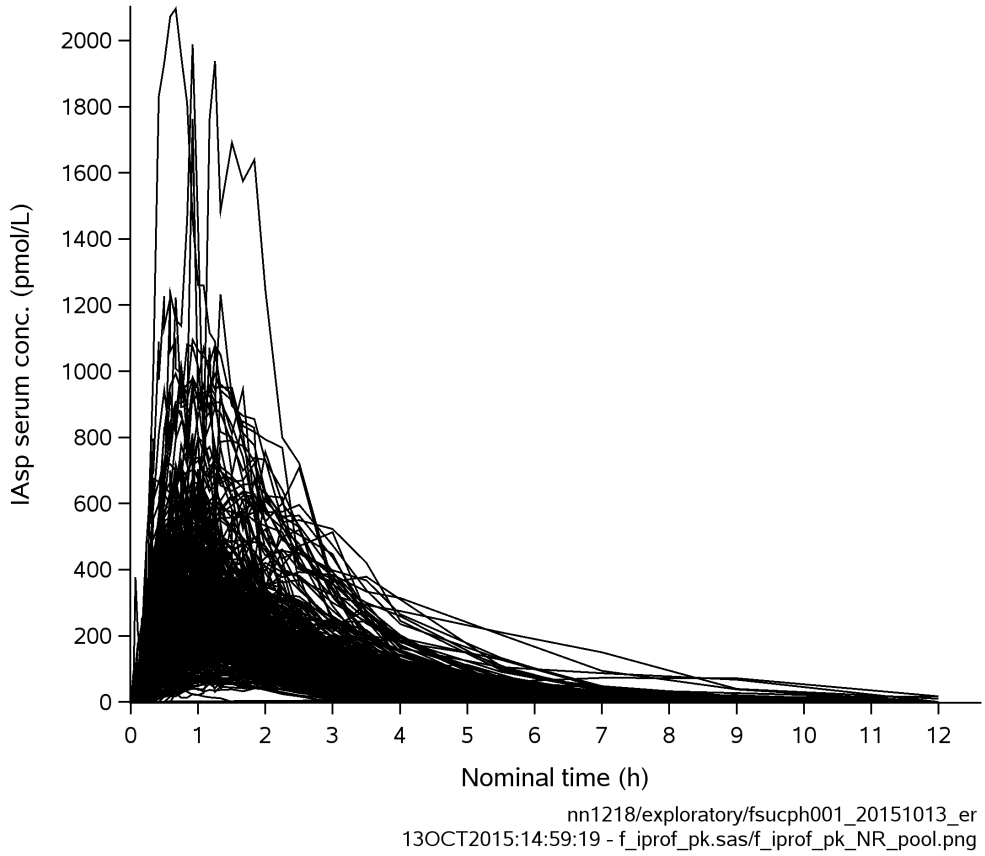
4: Mean PK profiles (0-6h) - adults, 0.2U/kg - trials 3887, 3888, 3889, 3891, 3921, 3978



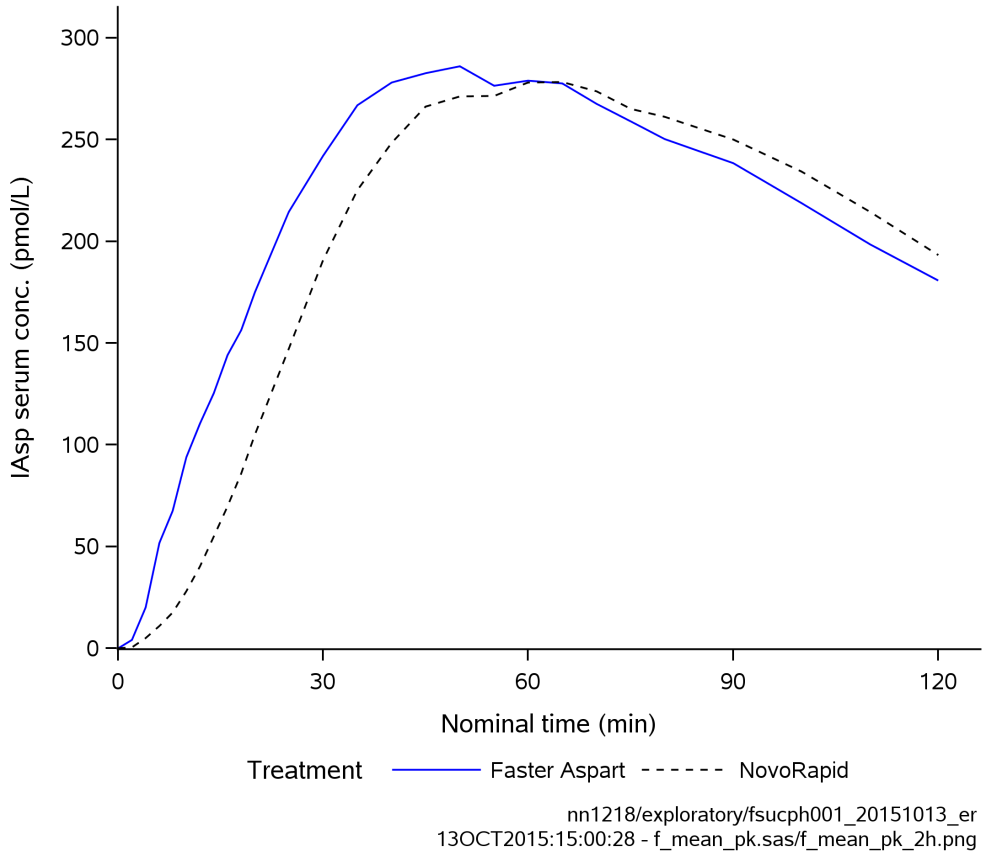
5: Mean GIR profiles (0-6h) - adults, 0.2U/kg - trials 3887, 3891 and 3978



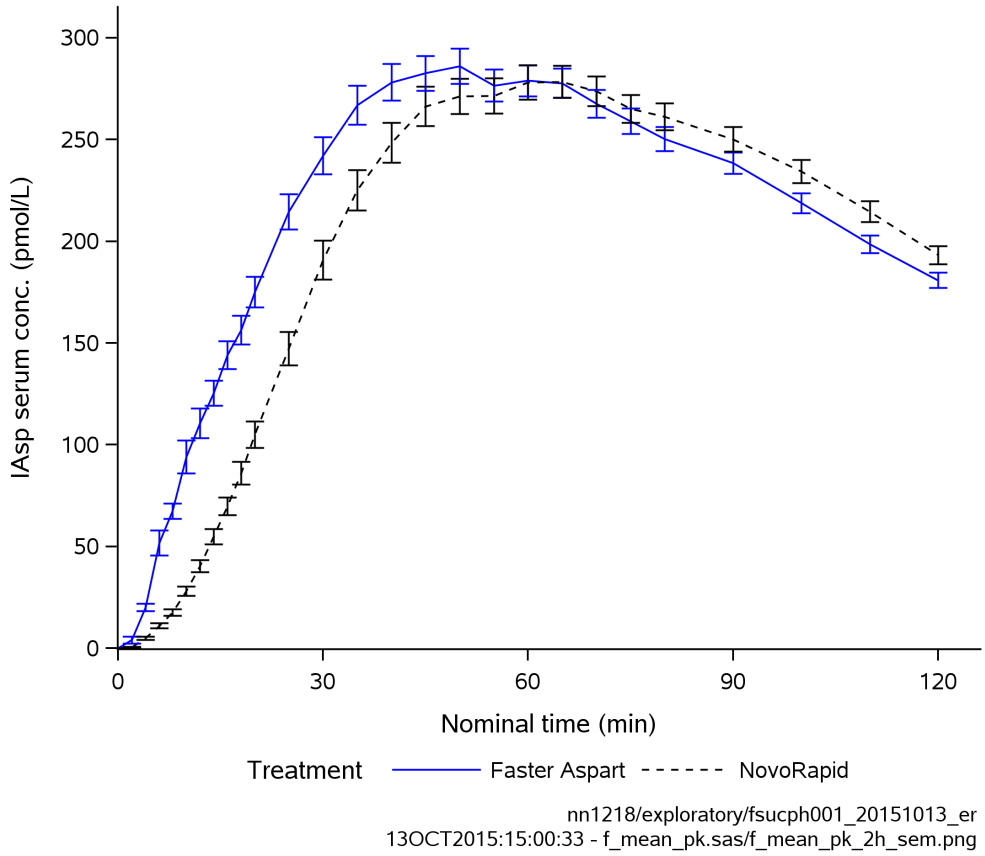
6: Insulin Aspart individual profiles - Faster Aspart - trials 3887,3888,3889,3891,3921,3978



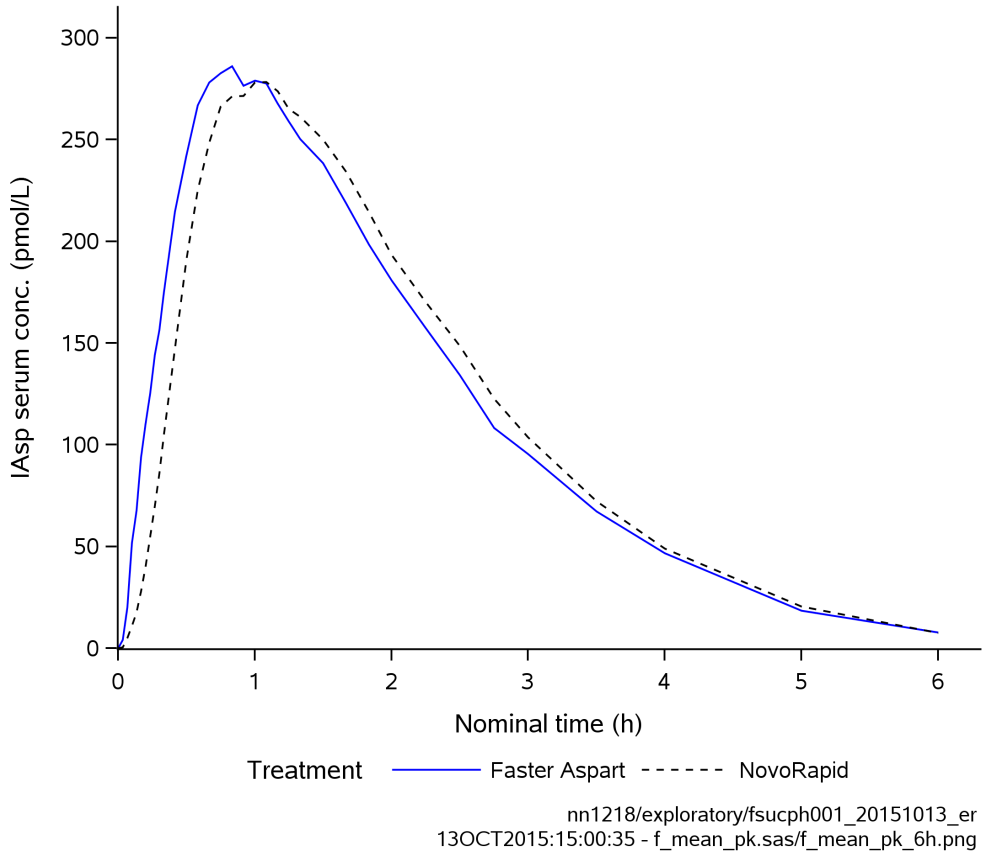
7: Insulin Aspart individual profiles - NovoRapid - trials 3887,3888,3889,3891,3921,3978



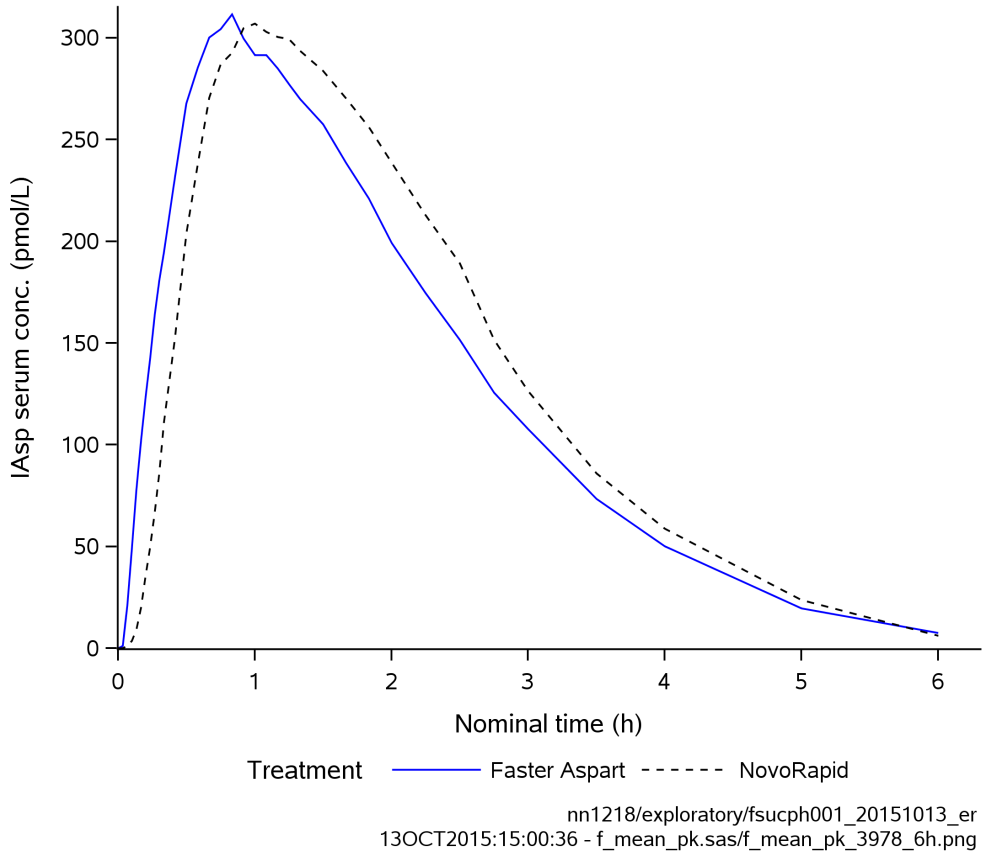
8: Insulin Aspart - mean profiles (0-2h) - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



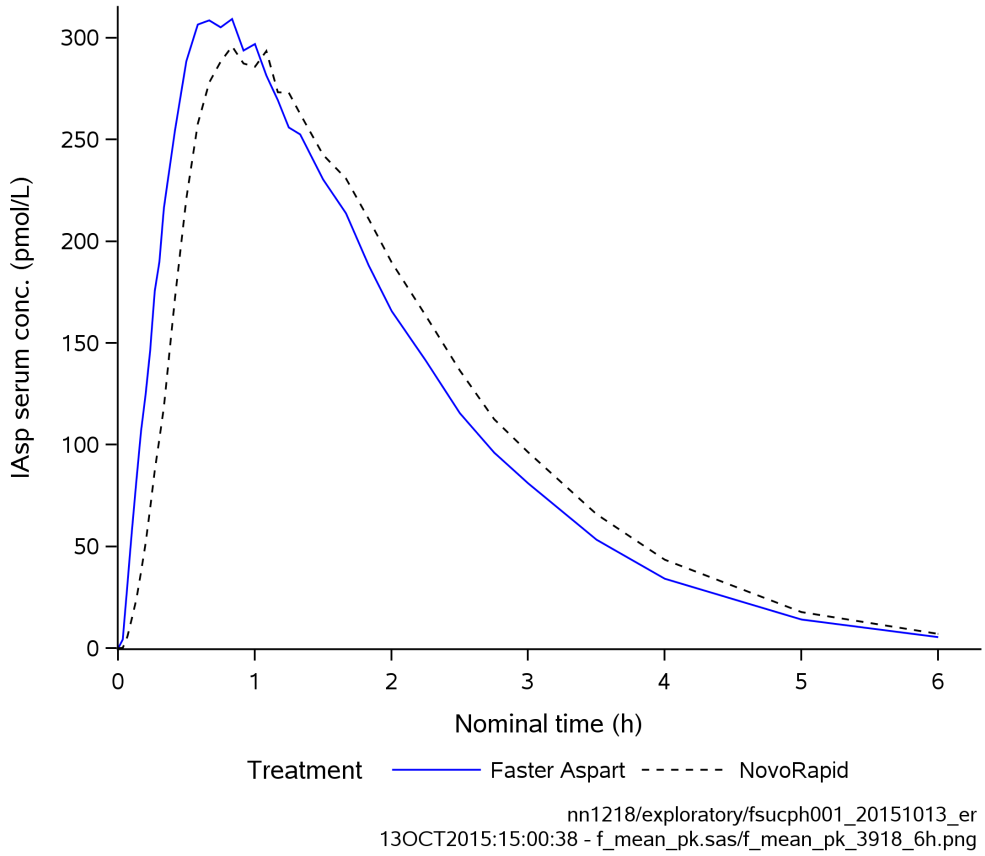
9: Insulin Aspart - mean (SEM) profiles (0-2h) - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



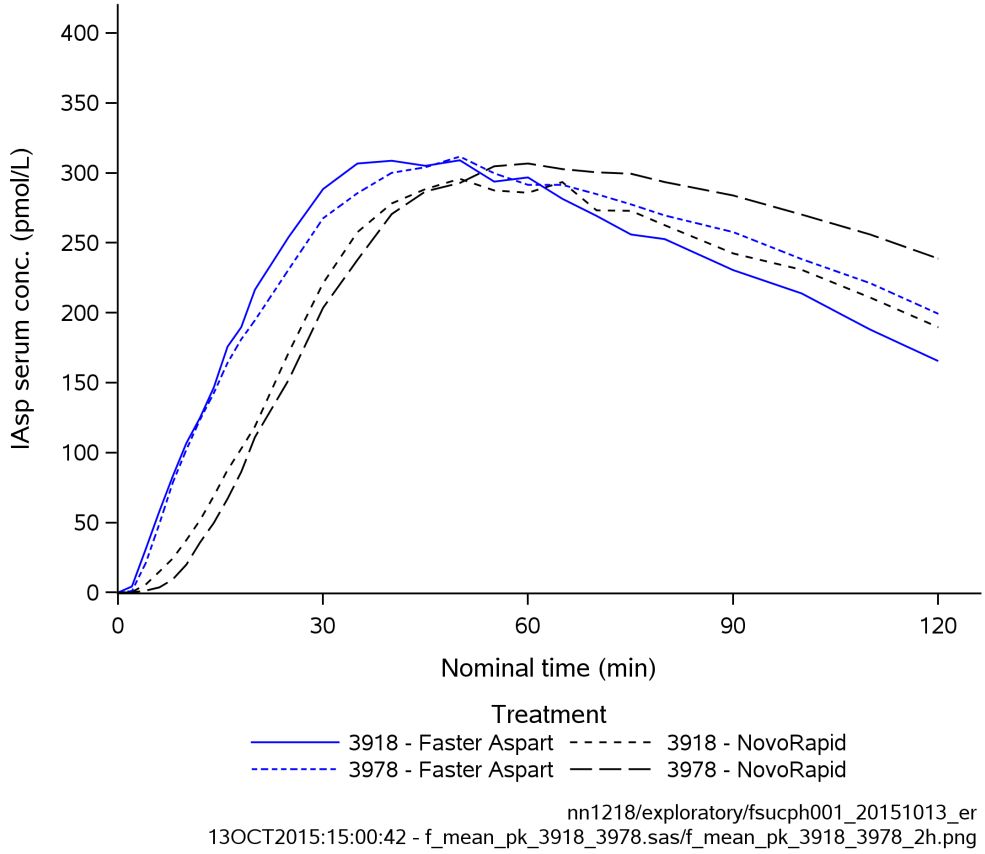
10: Insulin Aspart - mean profiles (0-6h) - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



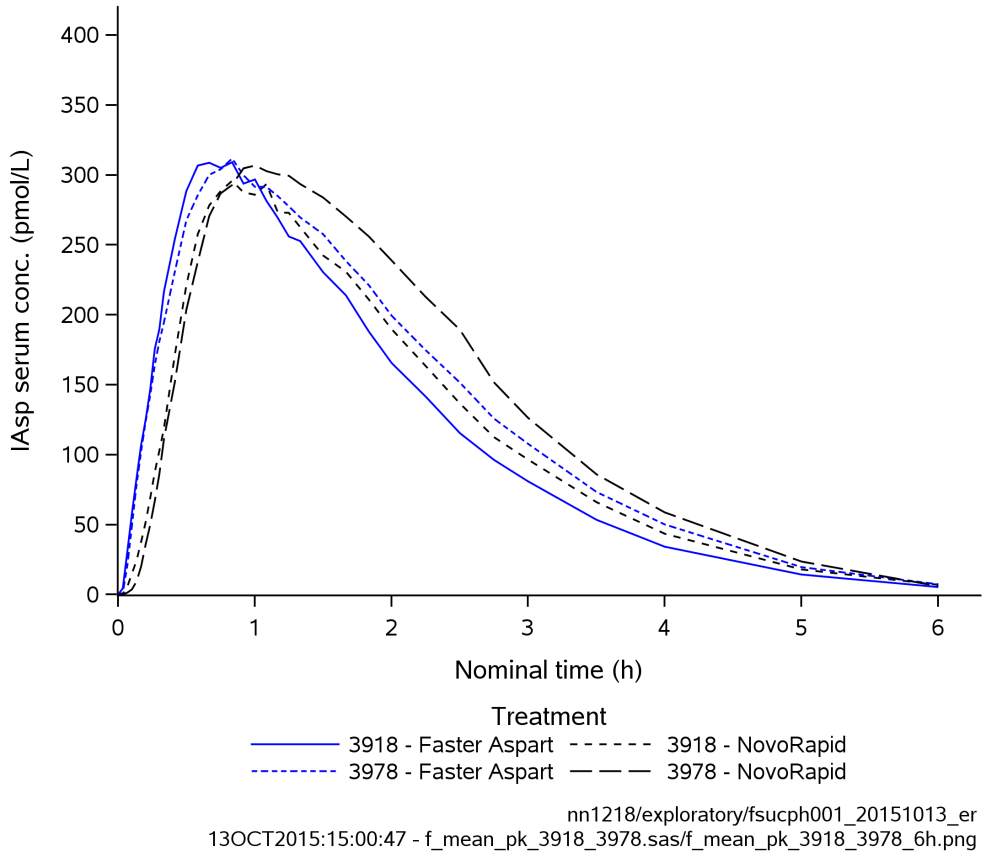
11: Insulin Aspart - mean profiles (0-6h) - trial 3978



12: Insulin Aspart - mean profiles (0-6h) - trial 3918



13: Insulin Aspart - mean profiles - trials 3918 and 3978



14: Insulin Aspart - mean profiles - trials 3918 and 3978

15: Insulin Aspart endpoints - time parameters - statistical analysis - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	SE	95% CI	P-value
Onset of appearance (min)					
LSMeans					
Faster Aspart	261	4.08	0.26		
NovoRapid	256	8.94	0.26		
Treatment Difference					
Faster Aspart - NovoRapid		-4.86		[-5.32;-4.39]	<0.001
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.46		[0.41;0.50]	
Time to 50% Cmax (min)					
LSMeans					
Faster Aspart	261	22.61	0.61		
NovoRapid	256	32.08	0.62		
Treatment Difference					
Faster Aspart - NovoRapid		-9.47		[-10.67;-8.26]	<0.001
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.70		[0.67;0.74]	
tmax (min)					
LSMeans					
Faster Aspart	261	62.43	1.69		
NovoRapid	256	69.76	1.70		
Treatment Difference					
Faster Aspart - NovoRapid		-7.33		[-11.09;-3.57]	<0.001
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.89		[0.84;0.95]	
Time to late 50% Cmax (min)					
LSMeans					
Faster Aspart	261	148.83	3.50		
NovoRapid	256	160.82	3.51		
Treatment Difference					
Faster Aspart - NovoRapid		-11.99		[-17.70;-6.28]	<0.001
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.93		[0.89;0.96]	
End of appearance (min)					
LSMeans					
Faster Aspart	259	361.08	6.97		
NovoRapid	256	370.17	6.98		
Treatment Difference					
Faster Aspart - NovoRapid		-9.09		[-20.09;1.92]	0.105
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.98		[0.95;1.01]	
t1/2 (min)					
LSMeans					
Faster Aspart	258	57.04	1.90		
NovoRapid	256	58.05	1.90		
Treatment Difference					
Faster Aspart - NovoRapid		-1.01		[-4.54;2.52]	0.575
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.98		[0.92;1.04]	

N: Number of profiles contributing to analysis,
SE: Standard error, CI: Confidence interval.
The endpoint was analysed in a linear mixed model with treatment and
period(trial) as fixed effects and subject(trial) as a random effect.
Ratios and the corresponding CIs were estimated using Fieller's method.
nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:24 - a_pk_add.sas/a_pk_add.txt

16: Insulin Aspart endpoints - time to late 50% Cmax - sensitivity analysis - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	SE	95% CI	P-value
Time to late 50% Cmax (min)					
LSMeans					
Faster Aspart	260	149.11	3.49		
NovoRapid	255	161.33	3.50		
Treatment Difference					
Faster Aspart - NovoRapid		-12.22		[-17.93;-6.50]	<0.001
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.92		[0.89;0.96]	

N: Number of profiles contributing to analysis,
SE: Standard error, CI: Confidence interval.
The endpoint was analysed in a linear mixed model with treatment and
period(trial) as fixed effects and subject(trial) as a random effect.
Ratios and the corresponding CIs were estimated using Fieller's method.
nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:25 - a_pk_add.sas/a_pk_add_sens.txt

17: Insulin Aspart endpoints - AUCIASP and Cmax - statistical analysis - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	95% CI	P-value
AUCIASP(0-15min) (pmol*h/L)				
LSMeans				
Faster Aspart	261	11.45		
NovoRapid	256	2.99		
Treatment Ratio				
Faster Aspart / NovoRapid		3.83	[3.41;4.29]	<0.001
AUCIASP(0-30min) (pmol*h/L)				
LSMeans				
Faster Aspart	261	52.12		
NovoRapid	256	25.92		
Treatment Ratio				
Faster Aspart / NovoRapid		2.01	[1.87;2.17]	<0.001
AUCIASP(0-1h) (pmol*h/L)				
LSMeans				
Faster Aspart	261	176.96		
NovoRapid	256	134.13		
Treatment Ratio				
Faster Aspart / NovoRapid		1.32	[1.26;1.39]	<0.001
AUCIASP(0-90min) (pmol*h/L)				
LSMeans				
Faster Aspart	261	299.51		
NovoRapid	256	257.63		
Treatment Ratio				
Faster Aspart / NovoRapid		1.16	[1.12;1.21]	<0.001
AUCIASP(0-2h) (pmol*h/L)				
LSMeans				
Faster Aspart	261	400.77		
NovoRapid	256	365.03		
Treatment Ratio				
Faster Aspart / NovoRapid		1.10	[1.06;1.14]	<0.001
AUCIASP(0-12h) (pmol*h/L)				
LSMeans				
Faster Aspart	260	676.91		
NovoRapid	256	670.37		
Treatment Ratio				
Faster Aspart / NovoRapid		1.01	[0.98;1.04]	0.470
AUCIASP(2-12h) (pmol*h/L)				
LSMeans				
Faster Aspart	260	240.30		
NovoRapid	256	263.68		
Treatment Ratio				
Faster Aspart / NovoRapid		0.91	[0.86;0.97]	0.003
Cmax (pmol/L)				
LSMeans				
Faster Aspart	261	297.66		
NovoRapid	256	287.25		

Treatment Ratio			
Faster Aspart / NovoRapid	1.04	[1.00;1.08]	0.085

Insulin Aspart endpoints - AUCIASP and Cmax -
statistical analysis - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	95% CI	P-value

N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was log-transformed and analysed in a linear mixed model with treatment and period(trial) as fixed effects and subject(trial) as a random effect.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:33 - a_pk_log.sas/a_pk_log.txt

18: Insulin Aspart endpoints - AUC(2-12h) - sensitivity analysis - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	95% CI	P-value
AUCIASP(2-12h) (pmol*h/L)				
LSMeans				
Faster Aspart	259	239.73		
NovoRapid	255	270.29		
Treatment Ratio				
Faster Aspart / NovoRapid		0.89	[0.85;0.93]	<0.001

N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was log-transformed and analysed in a linear mixed model with treatment and period(trial) as fixed effects and subject(trial) as a random effect.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:34 - a_pk_log.sas/a_pk_log_sens.txt

19: Insulin aspart dose adjusted AUCs and Cmax - treatment and BMI ratios - adults, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	95% CI	P-value
dose adjusted AUC(0-15min)(h/L)				
Faster Aspart	351			
NovoRapid	344			
Faster Aspart/NovoRapid - BMI 20		2.84	[2.28;3.53]	<0.001
Faster Aspart/NovoRapid - BMI 24		3.80	[3.40;4.24]	<0.001
Faster Aspart/NovoRapid - BMI 28		4.86	[4.04;5.85]	<0.001
BMI 20/BMI 24 - Faster Aspart		1.95	[1.53;2.49]	<0.001
BMI 20/BMI 24 - NovoRapid		2.61	[2.05;3.33]	<0.001
BMI 20/BMI 28 - Faster Aspart		3.43	[2.19;5.38]	<0.001
BMI 20/BMI 28 - NovoRapid		5.88	[3.75;9.23]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.76	[1.43;2.16]	<0.001
BMI 24/BMI 28 - NovoRapid		2.25	[1.83;2.77]	<0.001
Treatment*BMI Interaction				0.002
dose adjusted AUC(0-30min)(h/L)				
Faster Aspart	351			
NovoRapid	344			
Faster Aspart/NovoRapid - BMI 20		1.67	[1.44;1.93]	<0.001
Faster Aspart/NovoRapid - BMI 24		2.00	[1.86;2.16]	<0.001
Faster Aspart/NovoRapid - BMI 28		2.34	[2.07;2.65]	<0.001
BMI 20/BMI 24 - Faster Aspart		1.84	[1.53;2.22]	<0.001
BMI 20/BMI 24 - NovoRapid		2.21	[1.83;2.67]	<0.001
BMI 20/BMI 28 - Faster Aspart		3.08	[2.18;4.36]	<0.001
BMI 20/BMI 28 - NovoRapid		4.33	[3.06;6.12]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.68	[1.43;1.96]	<0.001
BMI 24/BMI 28 - NovoRapid		1.96	[1.67;2.29]	<0.001
Treatment*BMI Interaction				0.004
dose adjusted AUC(0-1h)(h/L)				
Faster Aspart	351			
NovoRapid	344			
Faster Aspart/NovoRapid - BMI 20		1.23	[1.11;1.37]	<0.001
Faster Aspart/NovoRapid - BMI 24		1.32	[1.26;1.39]	<0.001
Faster Aspart/NovoRapid - BMI 28		1.40	[1.28;1.53]	<0.001
BMI 20/BMI 24 - Faster Aspart		1.68	[1.45;1.95]	<0.001
BMI 20/BMI 24 - NovoRapid		1.80	[1.55;2.08]	<0.001
BMI 20/BMI 28 - Faster Aspart		2.60	[1.98;3.42]	<0.001
BMI 20/BMI 28 - NovoRapid		2.95	[2.25;3.88]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.55	[1.37;1.76]	<0.001
BMI 24/BMI 28 - NovoRapid		1.64	[1.45;1.86]	<0.001
Treatment*BMI Interaction				0.118
dose adjusted AUC(0-90min)(h/L)				
Faster Aspart	351			
NovoRapid	344			
Faster Aspart/NovoRapid - BMI 20		1.14	[1.05;1.24]	0.003
Faster Aspart/NovoRapid - BMI 24		1.17	[1.12;1.22]	<0.001
Faster Aspart/NovoRapid - BMI 28		1.19	[1.10;1.28]	<0.001
BMI 20/BMI 24 - Faster Aspart		1.55	[1.36;1.77]	<0.001
BMI 20/BMI 24 - NovoRapid		1.59	[1.39;1.81]	<0.001
BMI 20/BMI 28 - Faster Aspart		2.25	[1.77;2.86]	<0.001
BMI 20/BMI 28 - NovoRapid		2.35	[1.85;2.98]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.45	[1.30;1.62]	<0.001

BMI 24/BMI 28 - NovoRapid	1.48	[1.32;1.65]	<0.001
Treatment*BMI Interaction			0.544

Insulin aspart dose adjusted AUCs and Cmax - treatment and BMI ratios - adults, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	95% CI	P-value
dose adjusted AUC(0-2h)(h/L)				
Faster Aspart	351			
NovoRapid	344			
Faster Aspart/NovoRapid - BMI 20		1.09	[1.01;1.18]	0.032
Faster Aspart/NovoRapid - BMI 24		1.10	[1.06;1.15]	<0.001
Faster Aspart/NovoRapid - BMI 28		1.11	[1.04;1.19]	0.002
BMI 20/BMI 24 - Faster Aspart		1.45	[1.29;1.63]	<0.001
BMI 20/BMI 24 - NovoRapid		1.47	[1.30;1.65]	<0.001
BMI 20/BMI 28 - Faster Aspart		1.99	[1.60;2.48]	<0.001
BMI 20/BMI 28 - NovoRapid		2.03	[1.63;2.52]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.37	[1.24;1.51]	<0.001
BMI 24/BMI 28 - NovoRapid		1.38	[1.25;1.53]	<0.001
Treatment*BMI Interaction				0.764
dose adjusted AUC(0-12h)(h/L)				
Faster Aspart	350			
NovoRapid	344			
Faster Aspart/NovoRapid - BMI 20		1.04	[0.97;1.10]	0.265
Faster Aspart/NovoRapid - BMI 24		1.01	[0.98;1.05]	0.340
Faster Aspart/NovoRapid - BMI 28		1.00	[0.95;1.05]	0.940
BMI 20/BMI 24 - Faster Aspart		1.14	[1.04;1.24]	0.005
BMI 20/BMI 24 - NovoRapid		1.11	[1.02;1.22]	0.016
BMI 20/BMI 28 - Faster Aspart		1.27	[1.08;1.49]	0.005
BMI 20/BMI 28 - NovoRapid		1.22	[1.04;1.44]	0.016
BMI 24/BMI 28 - Faster Aspart		1.11	[1.03;1.20]	0.005
BMI 24/BMI 28 - NovoRapid		1.10	[1.02;1.18]	0.016
Treatment*BMI Interaction				0.447
dose adjusted Cmax(pmol/L)				
Faster Aspart	351			
NovoRapid	344			
Faster Aspart/NovoRapid - BMI 20		1.06	[0.97;1.15]	0.183
Faster Aspart/NovoRapid - BMI 24		1.04	[1.00;1.09]	0.058
Faster Aspart/NovoRapid - BMI 28		1.03	[0.96;1.10]	0.460
BMI 20/BMI 24 - Faster Aspart		1.50	[1.33;1.68]	<0.001
BMI 20/BMI 24 - NovoRapid		1.47	[1.31;1.66]	<0.001
BMI 20/BMI 28 - Faster Aspart		2.10	[1.69;2.62]	<0.001
BMI 20/BMI 28 - NovoRapid		2.04	[1.64;2.54]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.41	[1.27;1.55]	<0.001
BMI 24/BMI 28 - NovoRapid		1.39	[1.25;1.53]	<0.001
Treatment*BMI Interaction				0.649

N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was log-transformed and analysed in a linear mixed model with period(trial), treatment*dose-factor, treatment*log(BMI) as fixed effects and subject as a random effect.

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20: Insulin Aspart AUCs and Cmax - treatment and sex ratios adjusted for bodyweight (75 kg) - adults, trials 3887,3888,3889,3891,3921,3978

		N	Estimate	95% CI	P-value
AUCIASP(0-15min) (pmol*h/L)					
LSMeans					
Faster Aspart	Female	98	12.7988		
	Male	253	11.1226		
NovoRapid	Female	85	3.40512		
	Male	259	2.99947		
Ratios					
Faster Aspart/NovoRapid - Female			3.84	[3.09;4.78]	<0.001
Faster Aspart/NovoRapid - Male			3.79	[3.32;4.33]	<0.001
Female/Male - Faster Aspart			1.15	[0.81;1.63]	0.430
Female/Male - NovoRapid			1.14	[0.80;1.61]	0.477
Treatment*Sex					
Interaction					0.920
AUCIASP(0-30min) (pmol*h/L)					
LSMeans					
Faster Aspart	Female	98	56.9223		
	Male	253	50.7825		
NovoRapid	Female	85	26.7468		
	Male	259	26.5894		
Ratios					
Faster Aspart/NovoRapid - Female			2.17	[1.87;2.51]	<0.001
Faster Aspart/NovoRapid - Male			1.95	[1.78;2.13]	<0.001
Female/Male - Faster Aspart			1.12	[0.86;1.47]	0.406
Female/Male - NovoRapid			1.01	[0.77;1.32]	0.966
Treatment*Sex					
Interaction					0.231
AUCIASP(0-1h) (pmol*h/L)					
LSMeans					
Faster Aspart	Female	98	192.751		
	Male	253	172.053		
NovoRapid	Female	85	140.421		
	Male	259	135.918		
Ratios					
Faster Aspart/NovoRapid - Female			1.40	[1.26;1.55]	<0.001
Faster Aspart/NovoRapid - Male			1.29	[1.21;1.37]	<0.001
Female/Male - Faster Aspart			1.12	[0.91;1.38]	0.287
Female/Male - NovoRapid			1.03	[0.84;1.27]	0.760
Treatment*Sex					
Interaction					0.199
AUCIASP(0-90min) (pmol*h/L)					
LSMeans					

Faster Aspart	Female	98	327.095
	Male	253	291.464
NovoRapid	Female	85	275.263
	Male	259	259.503

Insulin Aspart AUCs and Cmax - treatment and sex ratios adjusted for bodyweight (75 kg) - adults, trials 3887,3888,3889,3891,3921,3978

		N	Estimate	95% CI	P-value
Ratios					
Faster Aspart/NovoRapid - Female			1.21	[1.11;1.32]	<0.001
Faster Aspart/NovoRapid - Male			1.15	[1.09;1.21]	<0.001
Female/Male - Faster Aspart			1.12	[0.94;1.35]	0.213
Female/Male - NovoRapid			1.06	[0.88;1.27]	0.524
Treatment*Sex					
Interaction					0.293
AUCIASP(0-2h) (pmol*h/L)					
LSMeans					
Faster Aspart	Female	98	443.566		
	Male	253	388.650		
NovoRapid	Female	85	396.956		
	Male	259	365.067		
Ratios					
Faster Aspart/NovoRapid - Female			1.14	[1.05;1.23]	0.001
Faster Aspart/NovoRapid - Male			1.09	[1.03;1.14]	<0.001
Female/Male - Faster Aspart			1.14	[0.97;1.35]	0.115
Female/Male - NovoRapid			1.09	[0.92;1.28]	0.318
Treatment*Sex					
Interaction					0.326
AUCIASP(0-12h) (pmol*h/L)					
LSMeans					
Faster Aspart	Female	97	753.802		
	Male	253	660.734		
NovoRapid	Female	85	757.197		
	Male	259	669.000		
Ratios					
Faster Aspart/NovoRapid - Female			1.02	[0.96;1.08]	0.542
Faster Aspart/NovoRapid - Male			1.01	[0.97;1.05]	0.556
Female/Male - Faster Aspart			1.14	[1.01;1.29]	0.035
Female/Male - NovoRapid			1.13	[1.00;1.28]	0.048
Treatment*Sex					
Interaction					0.835
Cmax (pmol/L)					
LSMeans					
Faster Aspart	Female	98	321.653		
	Male	253	290.844		
NovoRapid	Female	85	305.085		
	Male	259	292.690		
Ratios					
Faster Aspart/NovoRapid - Female			1.09	[1.00;1.18]	0.062
Faster Aspart/NovoRapid - Male			1.02	[0.97;1.08]	0.395

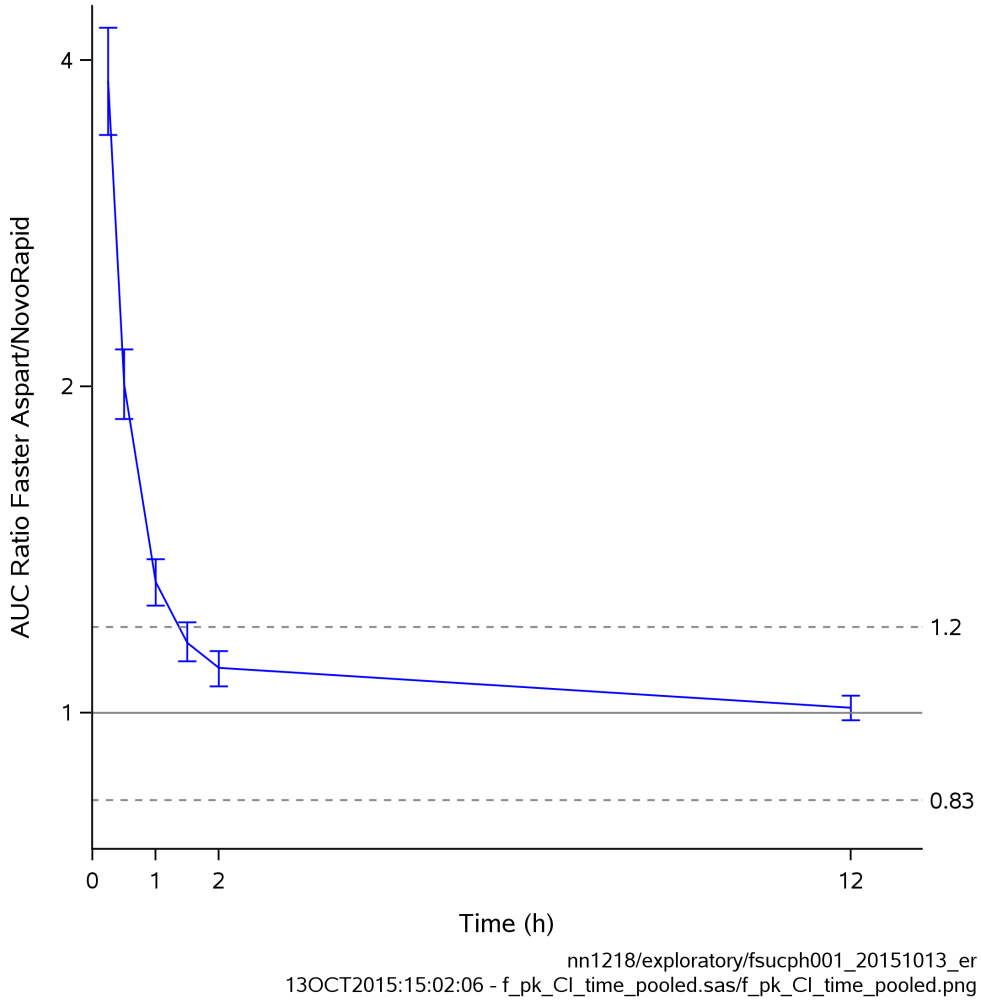
Female/Male - Faster Aspart	1.11	[0.94;1.31]	0.235
Female/Male - NovoRapid	1.04	[0.88;1.23]	0.625

Insulin Aspart AUCs and Cmax - treatment and sex ratios adjusted for bodyweight (75 kg) - adults, trials 3887,3888,3889,3891,3921,3978

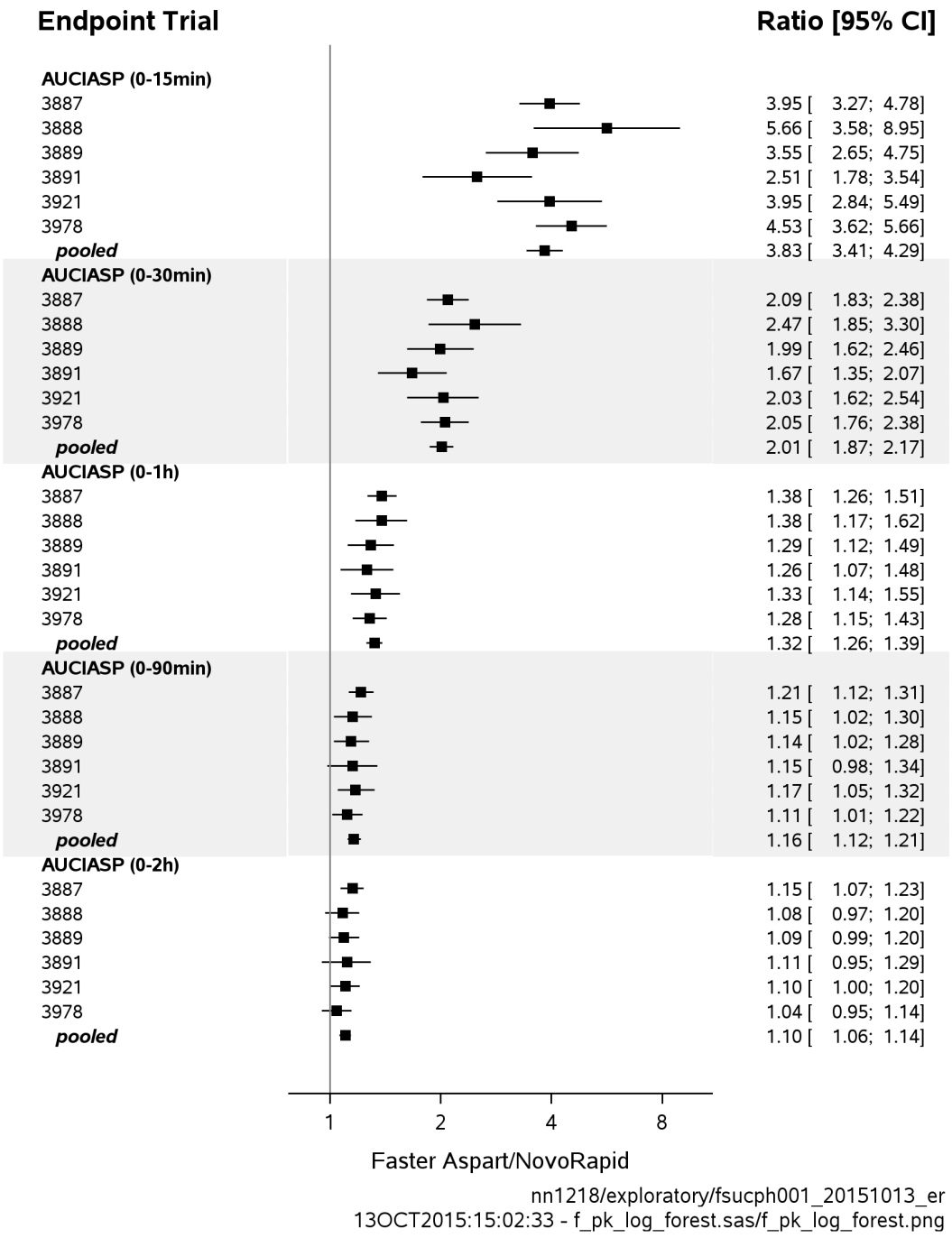
	N	Estimate	95% CI	P-value
Treatment*Sex Interaction				0.264

N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was log-transformed and analysed in a linear mixed model with period(trial), treatment*dose, treatment*sex , bodyweight as fixed effects and subject as a random effect.

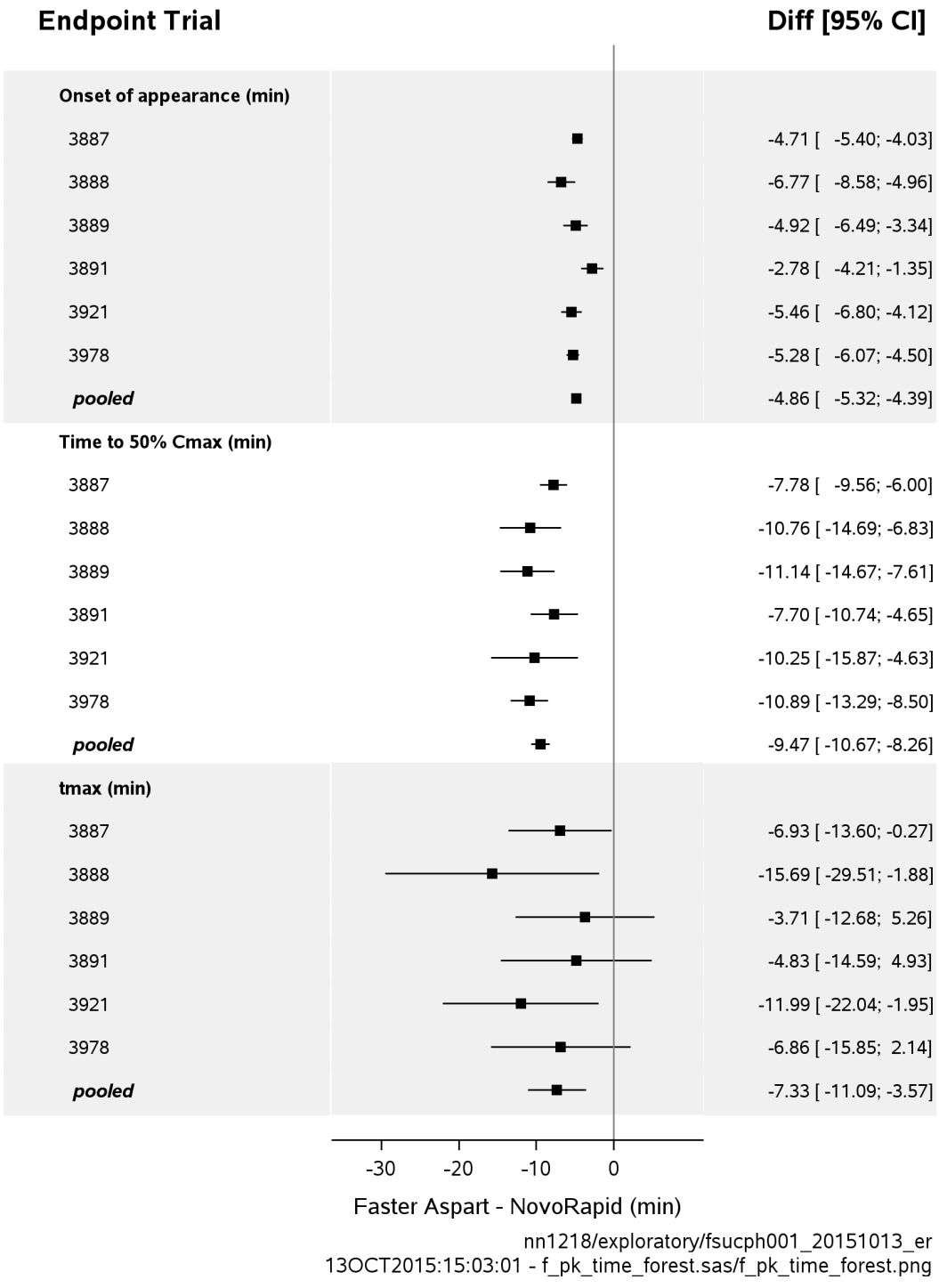
nn1218/exploratory/fsucph001_20151013_er
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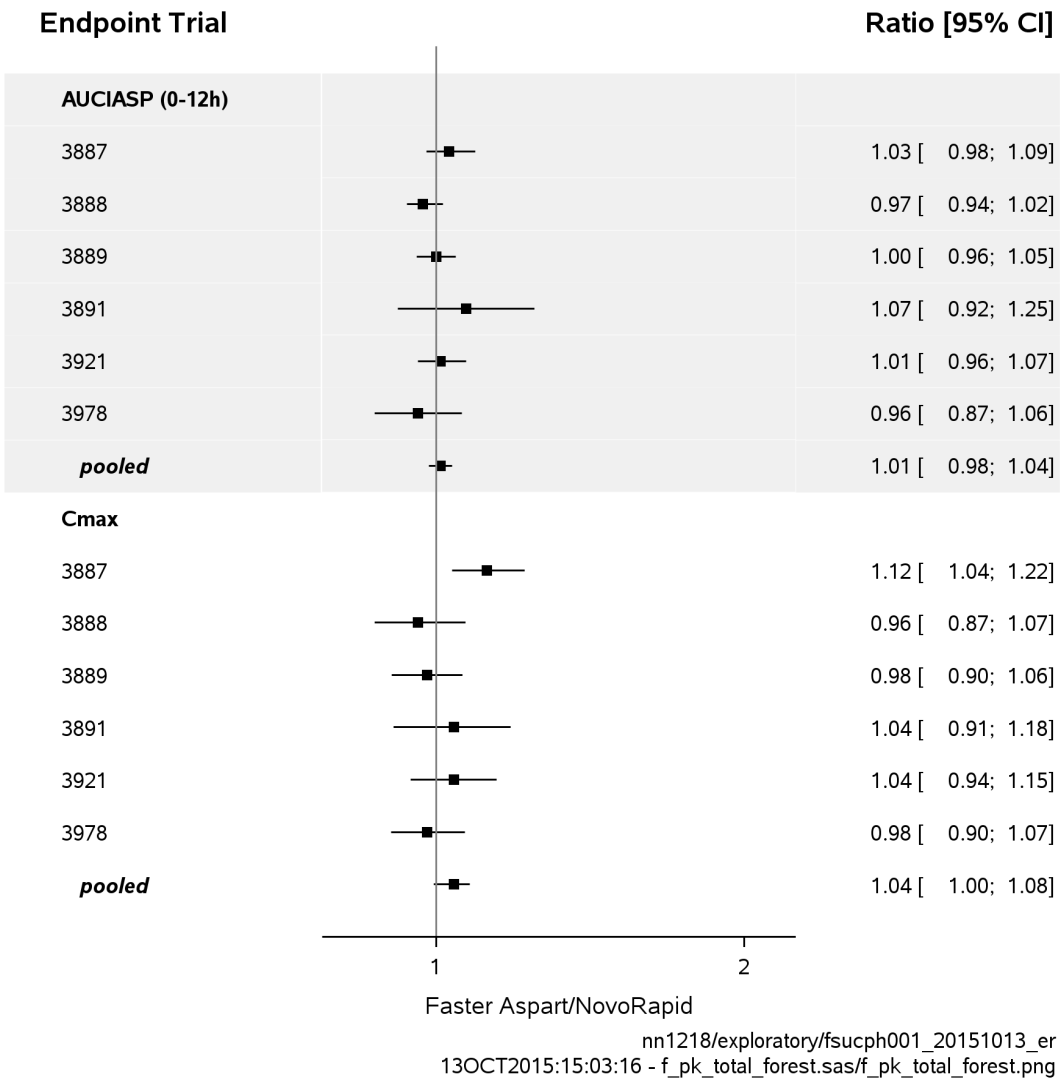
21: Insulin Aspart AUC ratios (95% CI) vs time - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



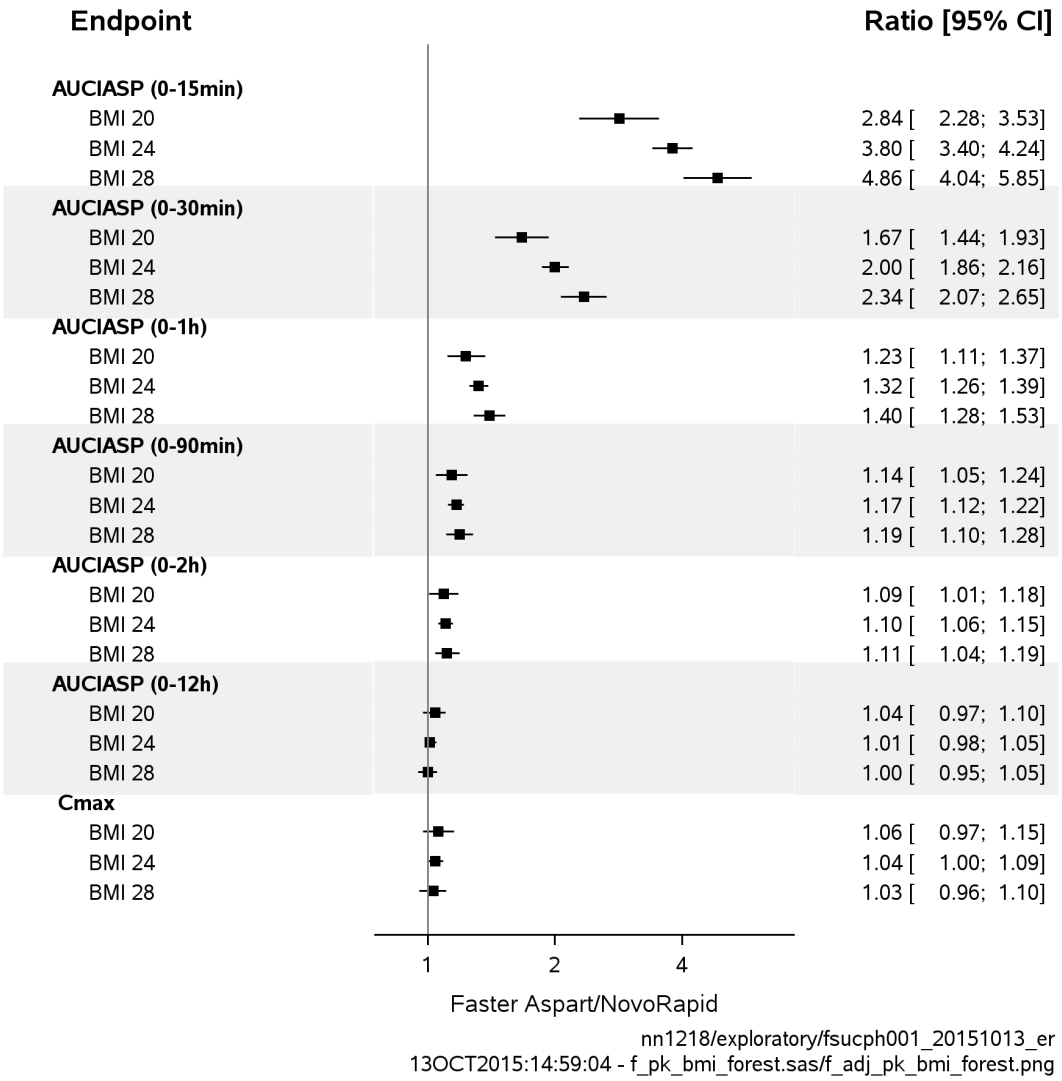
22: Insulin Aspart early AUCs by trial - treatment ratios - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



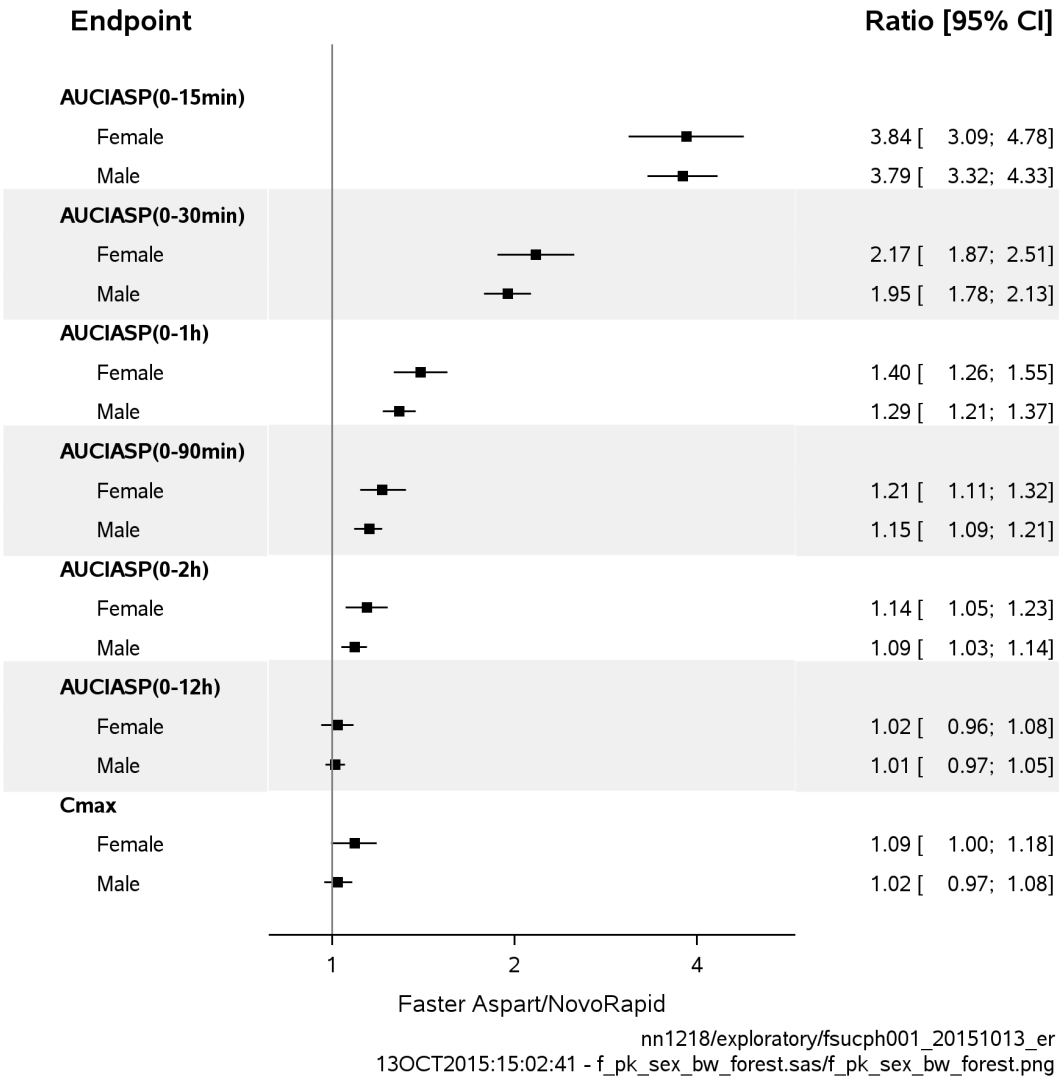
23: Insulin Aspart time parameters by trial - treatment differences - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



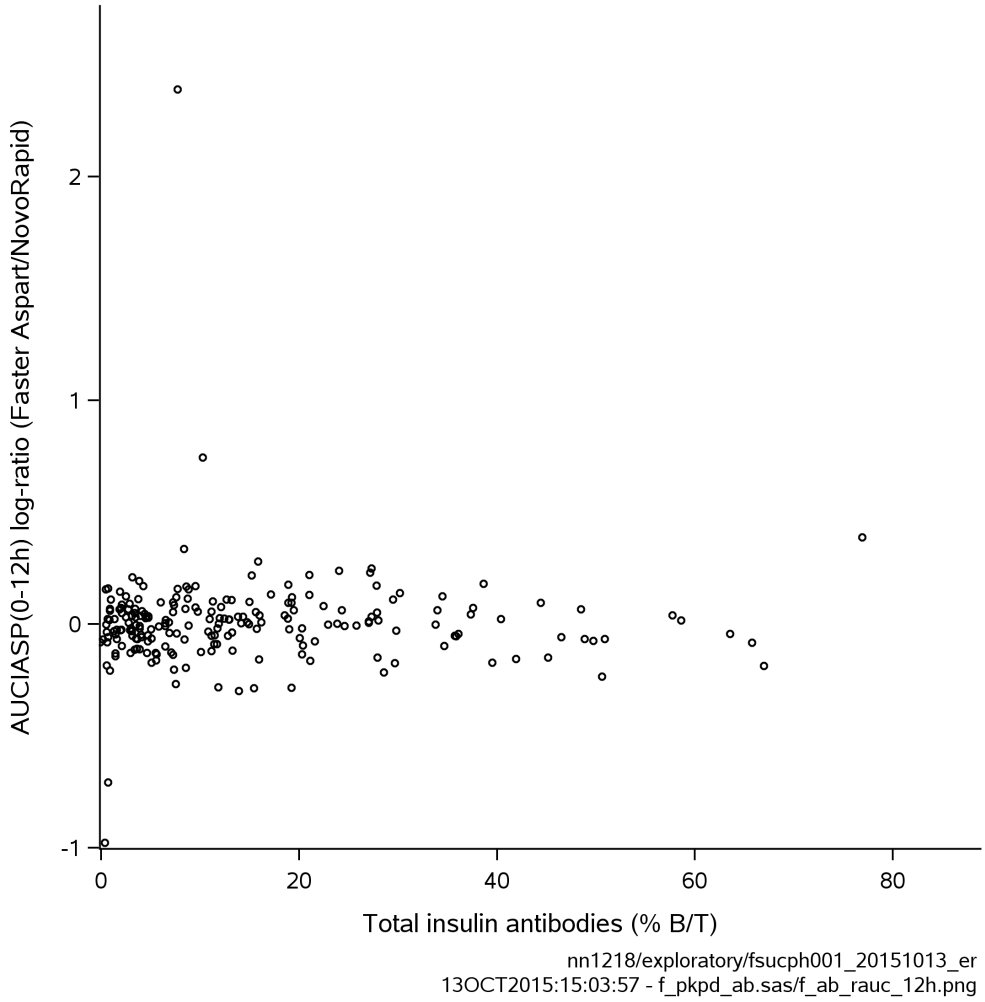
24: Insulin Aspart endpoints by trial AUC(0-12h) and cmax - treatment ratios - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



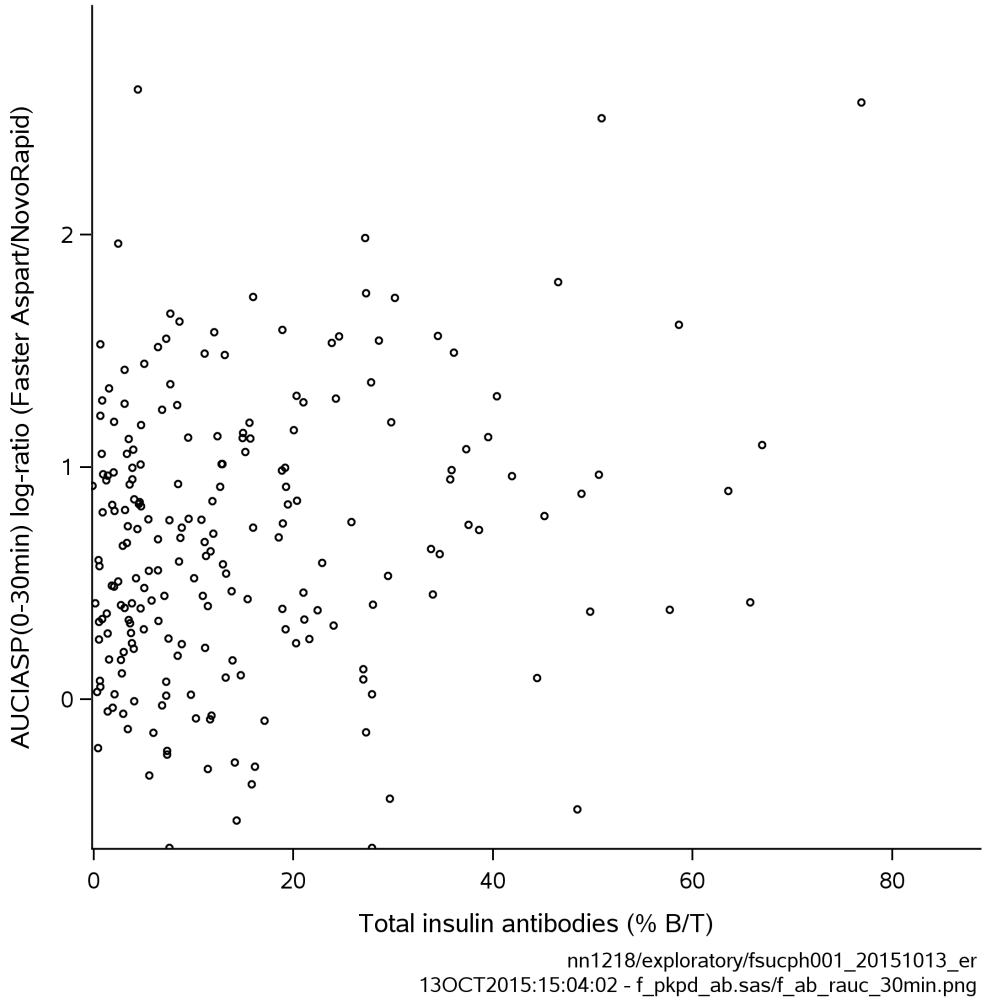
25: Dose adjusted PK endpoints by BMI - treatment ratios - adults, trials 3887, 3888, 3889, 3891, 3921, 3978



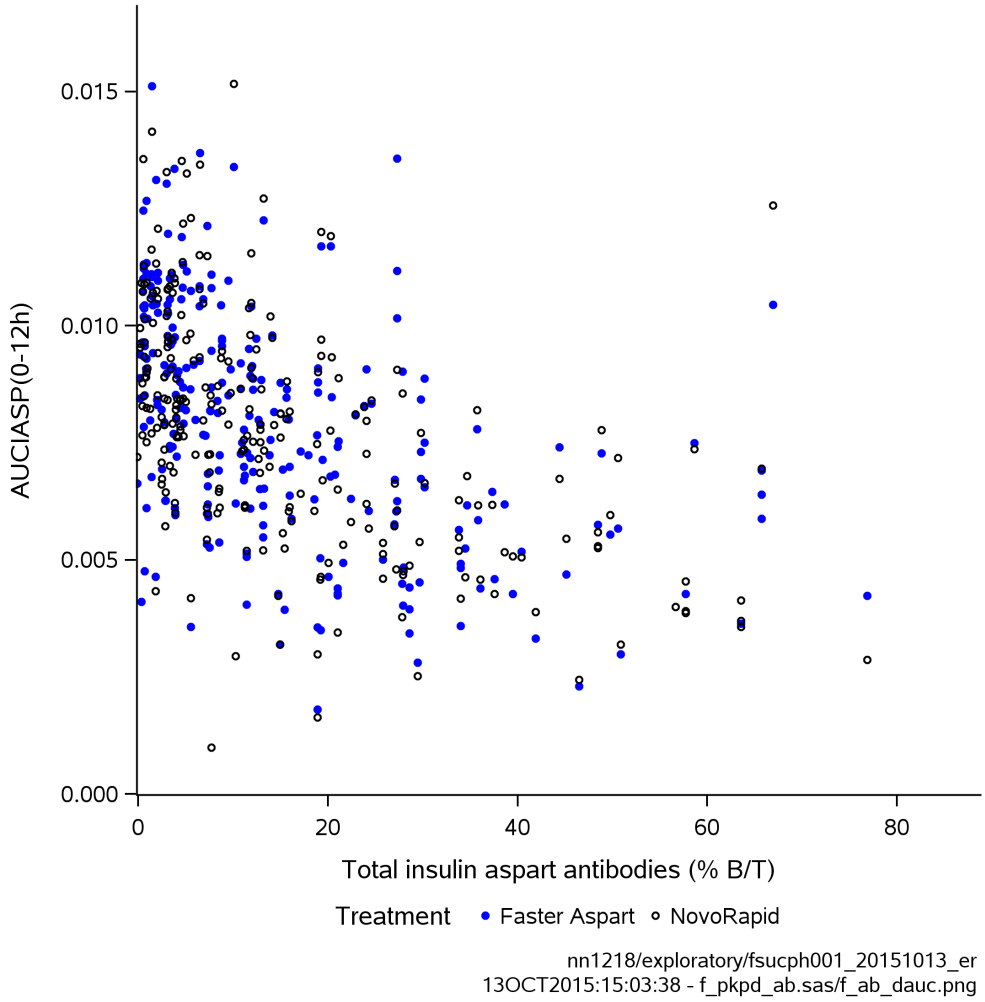
26: PK endpoints by sex adjusted for bodyweight - treatment ratios - adults, trials 3887, 3888, 3889, 3891, 3921, 3978



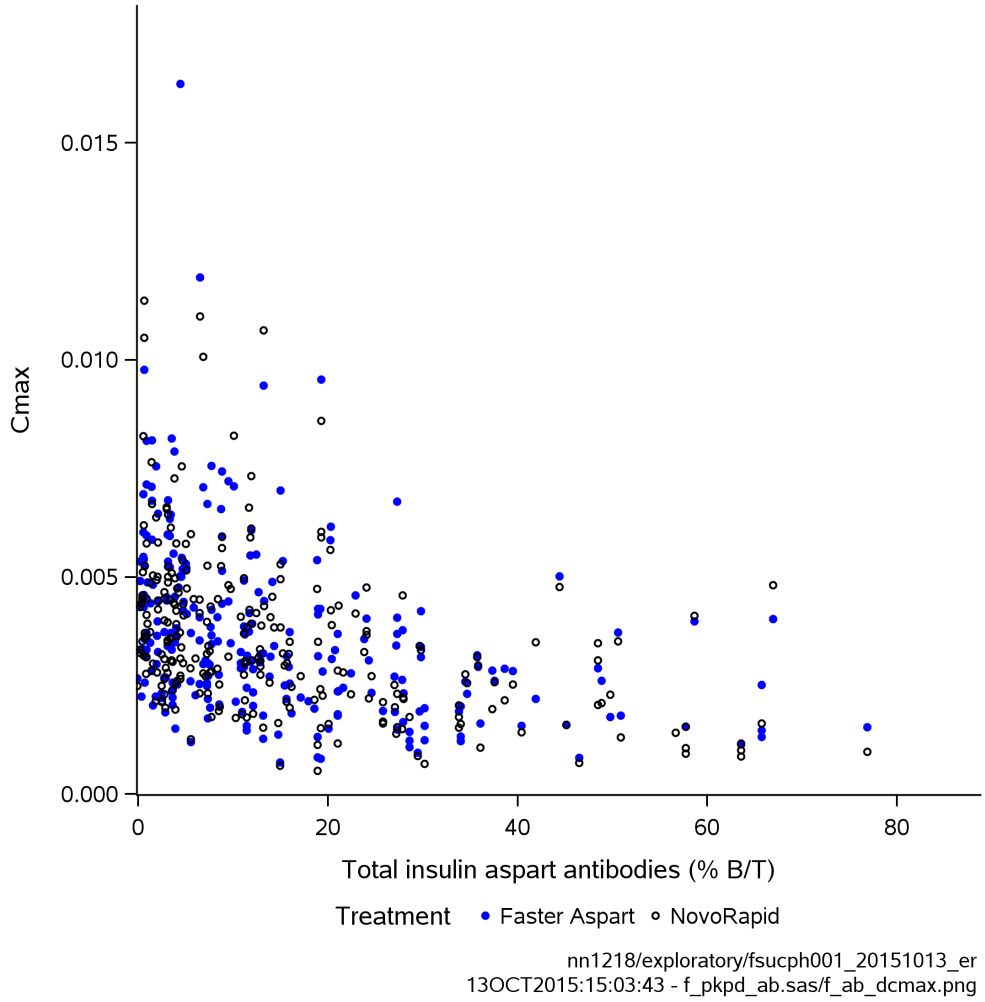
27: AUCIASP(0-12h) log treatment ratio vs antibodies - adults, trials 3887,3888,3889,3891,3921,3978



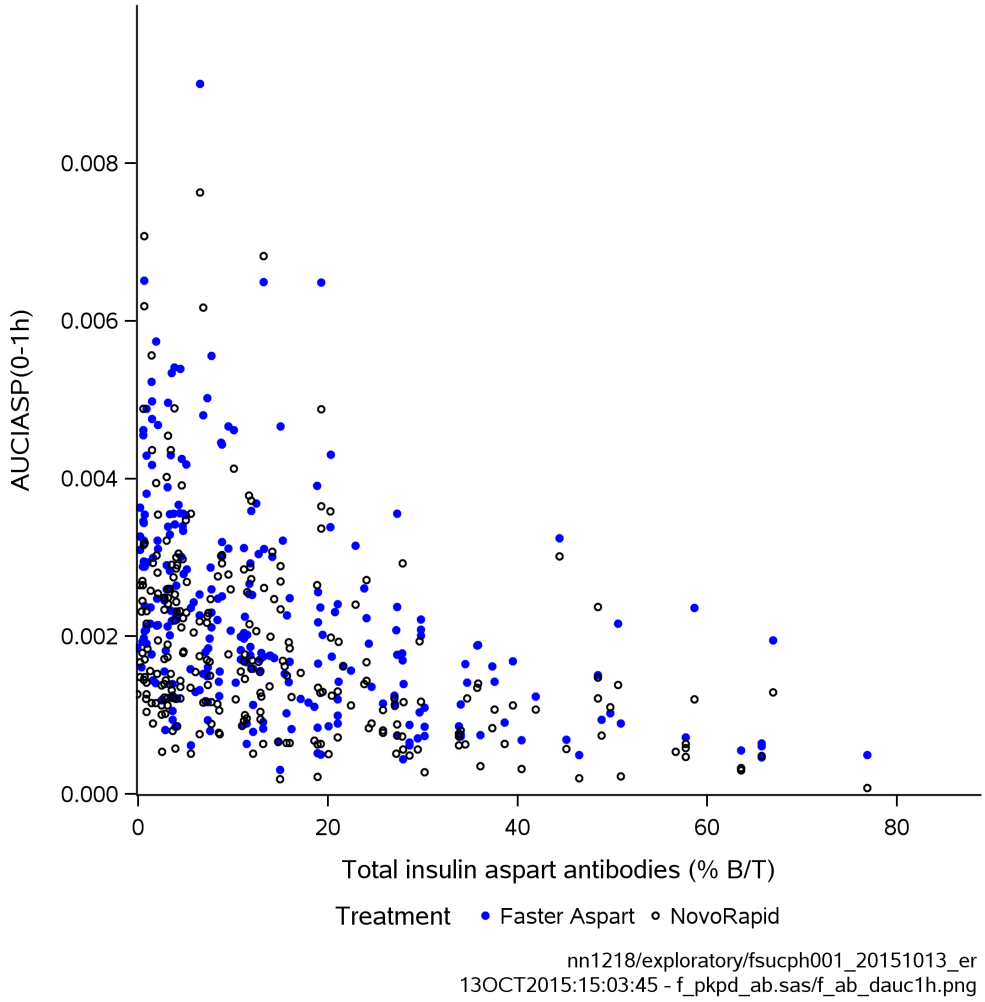
28: AUCIASP(0-30min) log treatment ratio vs antibodies - adults, trials 3887,3888,3889,3891,3921,3978



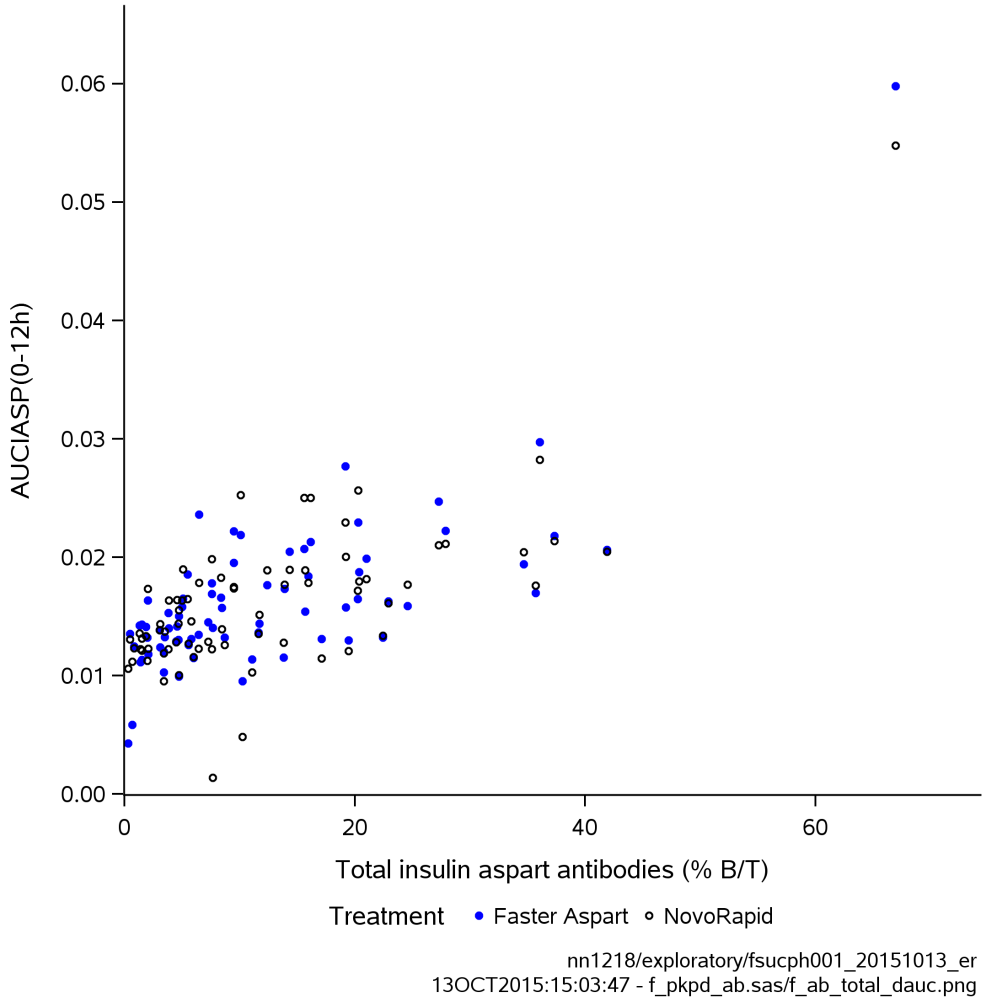
29: Dose adjusted AUCIASP(0-12h) vs antibodies - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



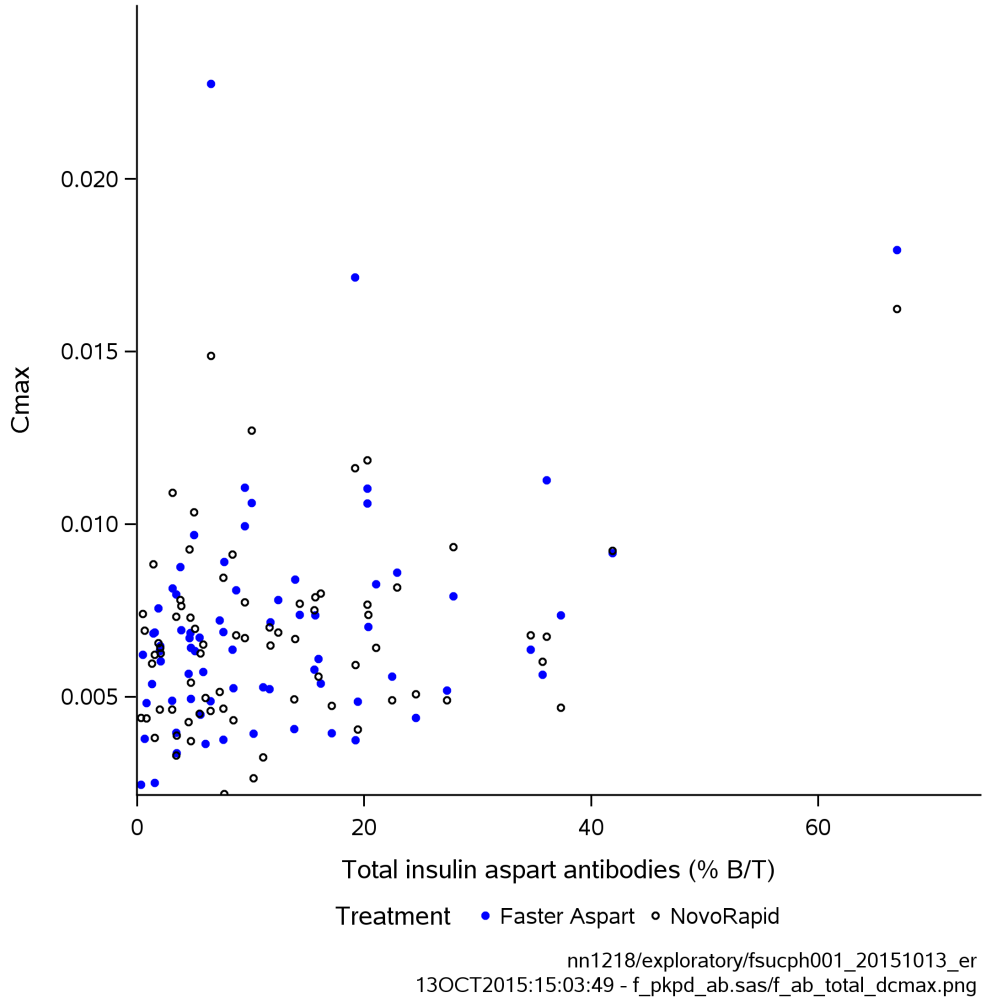
30: Dose adjusted IAsp Cmax vs antibodies - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



31: Dose adjusted AUCIASP(0-1h) vs antibodies - adults, 0.2 U/kg, trials 3887,3888,3889,3891,3921,3978



32: Dose adjusted total AUCIASP(0-12h) vs antibodies - adults, 0.2 U/kg, trials 3891,3978



33: Dose adjusted total IAsp Cmax vs antibodies - adults, 0.2 U/kg, trials 3891, 3978

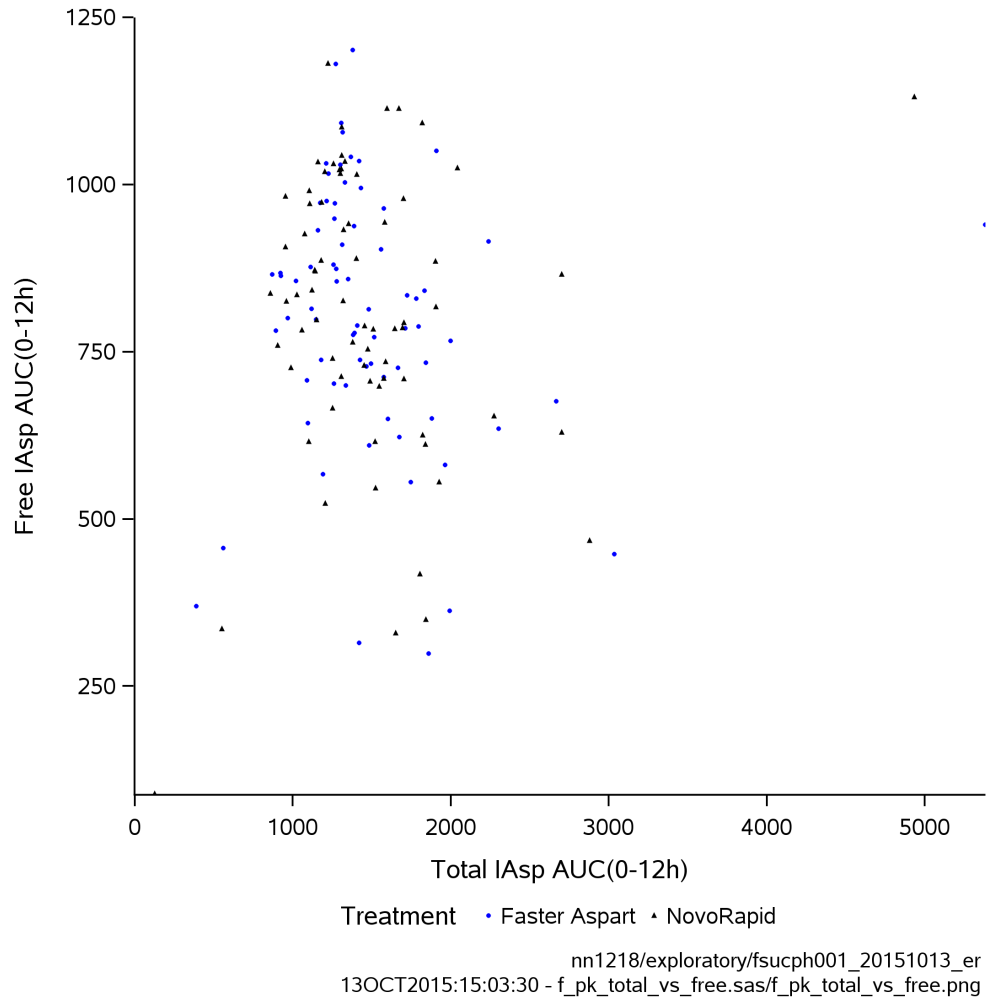
34: Free Insulin Aspart endpoints vs total insulin antibodies - AUCs and Cmax - - statistical analysis - adjusted for dose level and bodyweight - adults, trials 3887,3888,3889,3891,3921,3978

	N	Estimate	SE	95% CI	P-value
AUCIASP(0-30min) (pmol*h/L)					
Faster Aspart	351				
NovoRapid	344				
FA - ab 50th/25th percentile		0.7725	0.0272	[0.7322;0.8150]	<0.001
FA - ab 75th/25th percentile		0.5778	0.0578	[0.5156;0.6474]	<0.001
NR - ab 50th/25th percentile		0.7169	0.0270	[0.6797;0.7561]	<0.001
NR - ab 75th/25th percentile		0.4929	0.0575	[0.4402;0.5520]	<0.001
ab 25th percentile - FA/NR		1.8815	0.0408	[1.7366;2.0386]	<0.001
ab 50th percentile - FA/NR		2.0228	0.0370	[1.8808;2.1756]	<0.001
ab 75th percentile - FA/NR		2.2054	0.0461	[2.0144;2.4146]	<0.001
AUCIASP(0-1h) (pmol*h/L)					
Faster Aspart	351				
NovoRapid	344				
FA - ab 50th/25th percentile		0.8171	0.0214	[0.7834;0.8522]	<0.001
FA - ab 75th/25th percentile		0.6510	0.0454	[0.5953;0.7118]	<0.001
NR - ab 50th/25th percentile		0.7754	0.0213	[0.7437;0.8086]	<0.001
NR - ab 75th/25th percentile		0.5825	0.0452	[0.5329;0.6367]	<0.001
ab 25th percentile - FA/NR		1.2629	0.0285	[1.1942;1.3356]	<0.001
ab 50th percentile - FA/NR		1.3286	0.0259	[1.2627;1.3978]	<0.001
ab 75th percentile - FA/NR		1.4114	0.0322	[1.3249;1.5035]	<0.001
AUCIASP(0-12h) (pmol*h/L)					
Faster Aspart	350				
NovoRapid	344				
FA - ab 50th/25th percentile		0.8822	0.0129	[0.8601;0.9049]	<0.001
FA - ab 75th/25th percentile		0.7662	0.0274	[0.7259;0.8087]	<0.001
NR - ab 50th/25th percentile		0.8771	0.0128	[0.8552;0.8996]	<0.001
NR - ab 75th/25th percentile		0.7569	0.0273	[0.7173;0.7987]	<0.001
ab 25th percentile - FA/NR		1.0089	0.0174	[0.9750;1.0439]	0.611
ab 50th percentile - FA/NR		1.0145	0.0158	[0.9836;1.0464]	0.361
ab 75th percentile - FA/NR		1.0213	0.0196	[0.9827;1.0614]	0.283
Cmax (pmol/L)					
Faster Aspart	351				
NovoRapid	344				
FA - ab 50th/25th percentile		0.8612	0.0180	[0.8312;0.8922]	<0.001
FA - ab 75th/25th percentile		0.7279	0.0382	[0.6752;0.7848]	<0.001
NR - ab 50th/25th percentile		0.8423	0.0179	[0.8131;0.8725]	<0.001
NR - ab 75th/25th percentile		0.6944	0.0380	[0.6443;0.7484]	<0.001
ab 25th percentile - FA/NR		1.0204	0.0241	[0.9731;1.0700]	0.403
ab 50th percentile - FA/NR		1.0426	0.0219	[0.9986;1.0885]	0.058
ab 75th percentile - FA/NR		1.0697	0.0273	[1.0138;1.1286]	0.014

N: Number of profiles contributing to analysis.
SE: Standard error, CI: Confidence interval.
The log-transformed endpoint was analysed in a linear mixed model with dose(treatment) and period(trial) as fixed factors, log(bodyweight) and log(1+ab/13*) as covariates with treatment dependent slopes and subject(trial) as random effect.
Insulin antibody levels < 0 were set to 0.
*median from trial 3852 week 26

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35: Free vs. total AUCIASP(0-12 hours) - adults, dose 0.2 U/kg, trials 3891,3978

36: Pooled GIR data - baseline characteristics Trials 3887, 3891 (Younger adults) and 3978 (FIA(Q) and NovoRapid)

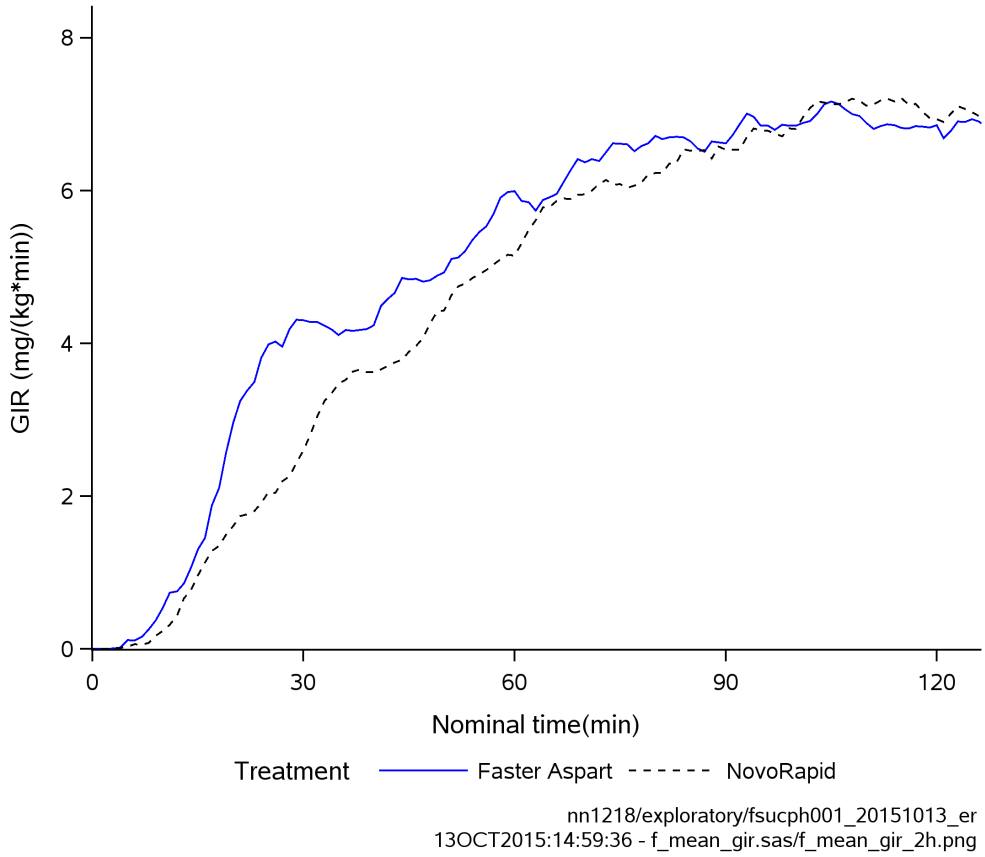
Trial	Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
Pooled	Both	Age (years)	119	20	28	39	39	47	61
		Weight (kg)	119	52.6	70.0	76.5	76.8	83.9	98.0
		BMI	119	18.9	23.0	24.5	24.5	26.3	28.7
		Total insulin aspart antibodies (% B/T)	119	0.16	3.49	9.49	14.11	20.37	66.94
	Male	Age (years)	92	21	29	40	40	48	60
		Weight (kg)	92	53.5	73.6	79.3	79.7	85.5	98.0
		BMI	92	18.9	23.5	24.9	24.8	26.4	28.7
		Total insulin aspart antibodies (% B/T)	92	0.16	3.70	8.65	14.52	20.64	66.94
	Female	Age (years)	27	20	25	37	37	47	61
		Weight (kg)	27	52.6	59.9	67.2	66.9	73.6	81.4
		BMI	27	19.3	21.0	23.5	23.3	25.3	28.0
		Total insulin aspart antibodies (% B/T)	27	0.16	2.03	11.44	12.71	20.37	37.31
NN1218-3887	Both	Age (years)	46	20	37	44	44	54	61
		Weight (kg)	46	52.6	70.0	77.1	77.4	85.4	95.3
		BMI	46	19.3	23.5	24.7	24.6	26.5	28.2
		Total insulin aspart antibodies (% B/T)	46	0.16	2.73	11.33	15.44	24.03	65.74
	Male	Age (years)	35	21	37	44	44	54	59
		Weight (kg)	35	61.0	74.2	80.8	81.0	90.4	95.3
		BMI	35	20.0	23.8	25.1	25.2	26.9	28.2
		Total insulin aspart antibodies (% B/T)	35	0.16	3.07	11.41	16.80	25.79	65.74
	Female	Age (years)	11	20	37	44	44	55	61
		Weight (kg)	11	52.6	59.9	67.2	66.1	73.4	78.2

Pooled GIR data - baseline characteristics
Trials 3887, 3891 (Younger adults) and 3978 (FIA(Q) and NovoRapid)

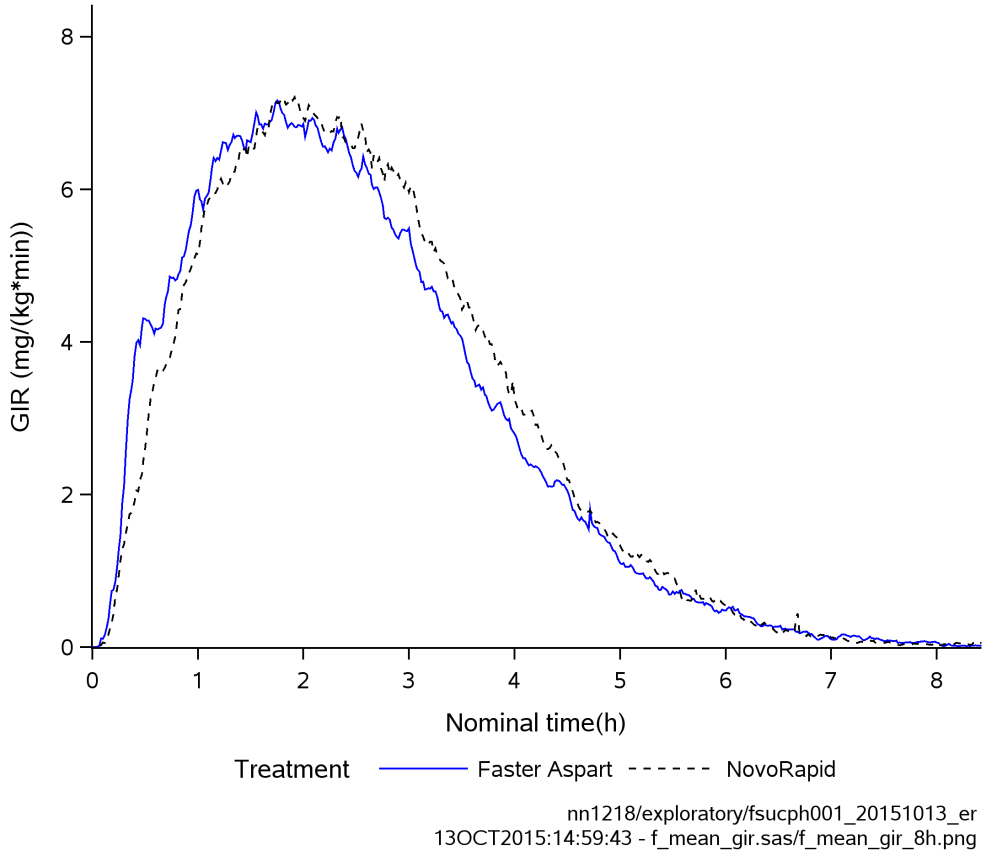
Trial	Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
NN1218-3887	Female	BMI	11	19.3	20.5	22.1	22.7	25.3	28.0
		Total insulin aspart antibodies (% B/T)	11	0.16	0.54	10.80	11.11	21.01	29.78
NN1218-3891	Both	Age (years)	22	22	24	26	27	30	34
		Weight (kg)	22	56.8	67.5	75.5	76.3	84.9	98.0
		BMI	22	20.7	23.4	24.5	24.7	26.7	27.9
		Total insulin aspart antibodies (% B/T)	22	0.84	3.95	10.47	14.16	21.09	46.50
	Male	Age (years)	15	22	24	26	27	30	34
		Weight (kg)	15	67.1	72.5	77.2	80.5	89.4	98.0
		BMI	15	20.7	23.4	25.1	24.8	26.6	27.9
		Total insulin aspart antibodies (% B/T)	15	1.91	3.95	8.59	15.43	27.02	46.50
	Female	Age (years)	7	23	23	25	27	30	34
		Weight (kg)	7	56.8	57.9	63.4	67.4	81.3	81.4
		BMI	7	20.9	22.2	23.6	24.6	27.7	27.8
		Total insulin aspart antibodies (% B/T)	7	0.84	2.03	11.44	11.44	17.91	24.27
NN1218-3978	Both	Age (years)	51	21	28	42	40	48	60
		Weight (kg)	51	53.3	71.2	76.5	76.4	83.2	96.9
		BMI	51	18.9	22.8	24.3	24.3	26.0	28.7
		Total insulin aspart antibodies (% B/T)	51	0.47	4.58	8.46	12.89	19.22	66.94
	Male	Age (years)	42	21	30	43	40	49	60
		Weight (kg)	42	53.5	72.6	78.7	78.3	83.9	96.9
		BMI	42	18.9	23.0	24.4	24.5	26.3	28.7

Pooled GIR data - baseline characteristics
Trials 3887, 3891 (Younger adults) and 3978 (FIA(Q) and NovoRapid)

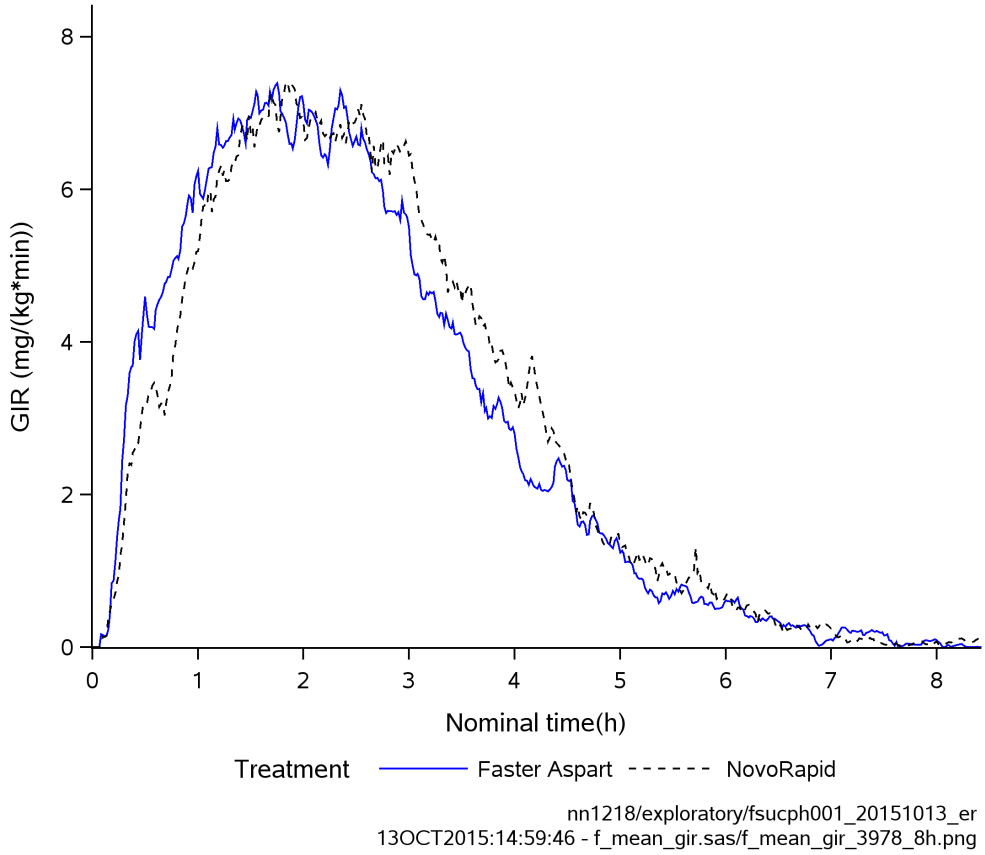
Trial	Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
NN1218-3978	Male	Total insulin aspart antibodies (% B/T)	42	0.47	3.86	7.99	12.29	15.95	66.94
	Female	Age (years)	9	23	27	41	37	47	51
		Weight (kg)	9	53.3	60.8	70.5	67.5	73.8	77.5
		BMI	9	19.7	21.0	24.2	23.1	24.6	25.4
		Total insulin aspart antibodies (% B/T)	9	1.53	5.08	19.19	15.66	20.37	37.31



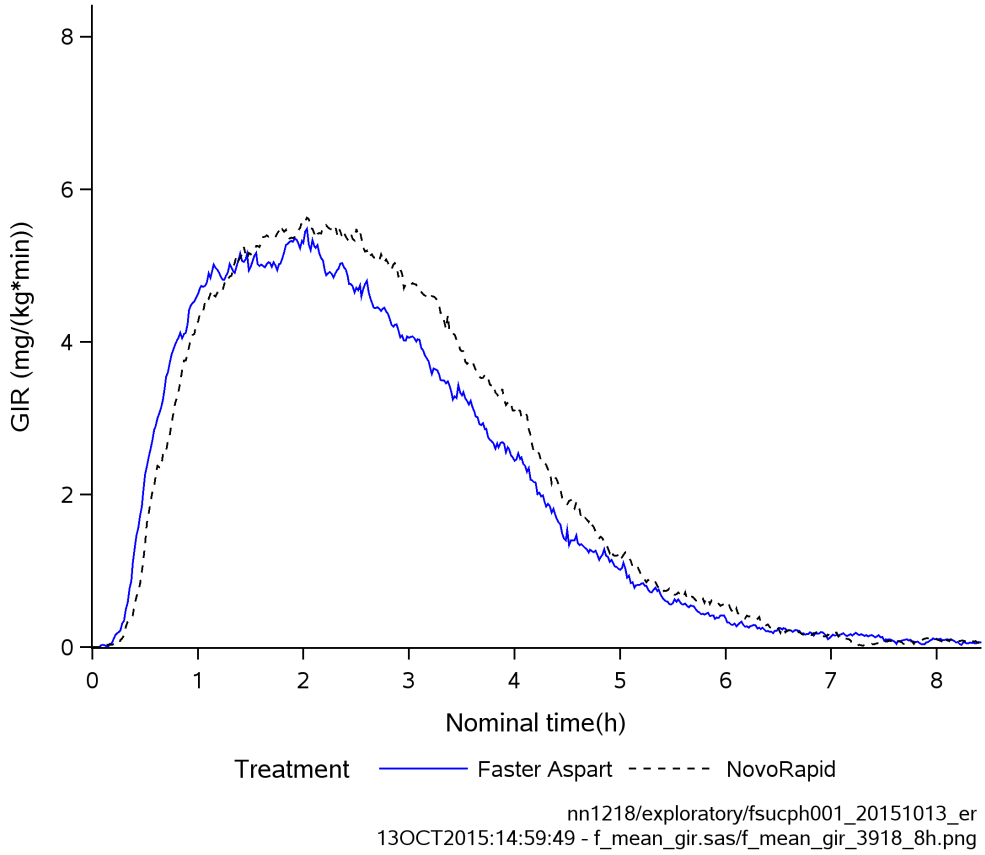
37: GIR - mean profiles (0-2 hours) - adults, 0.2 U/kg, trials 3887,3891,3978



38: GIR - mean profiles (0-8 hours) - adults, 0.2 U/kg, trials 3887,3891,3978



39: GIR - mean profiles (0-8 hours) - trial 3978



40: GIR - mean profiles (0-8 hours) - trial 3918

41: BG endpoint - onset of action - statistical analysis - adults, 0.2 U/kg, trials 3887,3891,3978

	N	Estimate	SE	95% CI	P-value
Onset of action (min)					
LSMeans					
Faster Aspart	162	16.06	0.75		
NovoRapid	160	20.97	0.76		
Treatment Difference					
Faster Aspart - NovoRapid		-4.91		[-6.86;-2.95]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.77		[0.69;0.85]	

N: Number of profiles contributing to analysis, CI: Confidence interval,
SE: Standard error of mean. The endpoint was analysed in a linear mixed model
with treatment and period as fixed effects and random subject effect.
Ratios and the corresponding CIs were estimated using Fieller's method.

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42: GIR endpoints - AUCGIR(0-30min), time to GIRmax, time to 50% GIRmax, time to late 50% GIRmax - statistical analysis - adults, 0.2 U/kg, trials 3887,3891,3978

	N	Estimate	SE	95% CI	P-value
AUCGIR(0-30min)(mg/kg)					
LSMeans					
Faster Aspart	163	51.16	2.54		
NovoRapid	160	29.42	2.55		
Treatment Difference					
Faster Aspart - NovoRapid		21.74		[15.55;27.93]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		1.74		[1.47;2.10]	
tGIRmax (min)					
LSMeans					
Faster Aspart	163	121.55	3.43		
NovoRapid	160	132.05	3.44		
Treatment Difference					
Faster Aspart - NovoRapid		-10.50		[-16.98;-4.02]	0.002
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.92		[0.87;0.97]	
Time to 50% GIRmax (min)					
LSMeans					
Faster Aspart	163	36.25	1.35		
NovoRapid	160	45.71	1.36		
Treatment Difference					
Faster Aspart - NovoRapid		-9.46		[-12.49;-6.42]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.79		[0.73;0.86]	
Time to late 50% GIRmax (min)					
LSMeans					
Faster Aspart	163	229.85	4.75		
NovoRapid	160	244.14	4.76		
Treatment Difference					
Faster Aspart - NovoRapid		-14.30		[-22.08;-6.52]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.94		[0.91;0.97]	

N: Number of profiles contributing to analysis, CI: Confidence interval,
SE: Standard error of mean. The endpoint was analysed in a linear mixed model
with treatment and period as fixed effects and random subject effect.
Ratios and the corresponding CIs were estimated using Fieller's method.

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43: GIR endpoints - AUCGIR and GIRmax - statistical analysis - adults, 0.2 U/kg, trials 3887,3891,3978

	N	Estimate	95% CI	P-value
AUCGIR(0-1h)(mg/kg)				
LSMeans				
Faster Aspart	163	179.51		
NovoRapid	160	134.38		
Treatment Ratio				
Faster Aspart / NovoRapid		1.34	[1.25;1.43]	<0.001
AUCGIR(0-90min)(mg/kg)				
LSMeans				
Faster Aspart	163	358.53		
NovoRapid	160	300.89		
Treatment Ratio				
Faster Aspart / NovoRapid		1.19	[1.13;1.26]	<0.001
AUCGIR(0-2h)(mg/kg)				
LSMeans				
Faster Aspart	163	556.84		
NovoRapid	160	494.02		
Treatment Ratio				
Faster Aspart / NovoRapid		1.13	[1.07;1.19]	<0.001
AUCGIR(0-12h)(mg/kg)				
LSMeans				
Faster Aspart	163	1344.39		
NovoRapid	160	1367.22		
Treatment Ratio				
Faster Aspart / NovoRapid		0.98	[0.94;1.03]	0.426
AUCGIR(2-12h)(mg/kg)				
LSMeans				
Faster Aspart	163	747.85		
NovoRapid	160	834.02		
Treatment Ratio				
Faster Aspart / NovoRapid		0.90	[0.85;0.95]	<0.001
GIRmax (mg/(kg*min))				
LSMeans				
Faster Aspart	163	7.10		
NovoRapid	160	7.06		
Treatment Ratio				
Faster Aspart / NovoRapid		1.01	[0.96;1.05]	0.814

N: Number of profiles contributing to analysis, CI: Confidence interval.
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect.

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44: GIR AUCs and GIRmax - treatment and sex ratios adjusted for bodyweight (75 kg) - adults, trials 3887,3891,3978

		N	Estimate	95% CI	P-value
AUCGIR(0-1h)(mg/kg)					
LSMeans					
Faster Aspart	Female	61	166.92		
	Male	192	181.37		
NovoRapid	Female	49	117.50		
	Male	198	139.89		
Ratios					
Faster Aspart/NovoRapid - Female			1.42	[1.24;1.61]	<0.001
Faster Aspart/NovoRapid - Male			1.29	[1.20;1.39]	<0.001
Female/Male - Faster Aspart			0.92	[0.76;1.12]	0.407
Female/Male - NovoRapid			0.84	[0.69;1.02]	0.085
Treatment*Sex					
Interaction					0.235
AUCGIR(0-90min)(mg/kg)					
LSMeans					
Faster Aspart	Female	61	323.48		
	Male	192	361.53		
NovoRapid	Female	49	253.99		
	Male	199	310.17		
Ratios					
Faster Aspart/NovoRapid - Female			1.27	[1.13;1.42]	<0.001
Faster Aspart/NovoRapid - Male			1.16	[1.08;1.24]	<0.001
Female/Male - Faster Aspart			0.89	[0.74;1.09]	0.264
Female/Male - NovoRapid			0.82	[0.67;1.00]	0.048
Treatment*Sex					
Interaction					0.196
AUCGIR(0-2h)(mg/kg)					
LSMeans					
Faster Aspart	Female	61	496.97		
	Male	192	557.47		
NovoRapid	Female	49	410.06		
	Male	199	504.18		
Ratios					
Faster Aspart/NovoRapid - Female			1.20	[1.07;1.34]	0.002
Faster Aspart/NovoRapid - Male			1.10	[1.03;1.17]	0.006
Female/Male - Faster Aspart			0.89	[0.74;1.08]	0.230
Female/Male - NovoRapid			0.81	[0.67;0.98]	0.033
Treatment*Sex					
Interaction					0.166
AUCGIR(0-12h)(mg/kg)					
LSMeans					

Faster Aspart	Female	61	1167.66
	Male	192	1345.01
NovoRapid	Female	49	1214.07
	Male	199	1362.40

GIR AUCs and GIRmax - treatment and sex ratios adjusted for bodyweight (75 kg) - adults, trials 3887,3891,3978

		N	Estimate	95% CI	P-value
Ratios					
Faster Aspart/NovoRapid - Female			0.97	[0.87;1.07]	0.495
Faster Aspart/NovoRapid - Male			0.99	[0.93;1.05]	0.762
Female/Male - Faster Aspart			0.87	[0.76;0.99]	0.042
Female/Male - NovoRapid			0.89	[0.78;1.02]	0.101
Treatment*Sex					
Interaction					0.659
GIRmax (mg/(kg*min))					
LSMeans					
Faster Aspart	Female	61	6.18		
	Male	192	7.05		
NovoRapid	Female	49	6.01		
	Male	199	7.09		
Ratios					
Faster Aspart/NovoRapid - Female			1.03	[0.93;1.14]	0.582
Faster Aspart/NovoRapid - Male			0.99	[0.94;1.05]	0.845
Female/Male - Faster Aspart			0.88	[0.75;1.02]	0.091
Female/Male - NovoRapid			0.85	[0.73;0.99]	0.035
Treatment*Sex					
Interaction					0.564

N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was log-transformed and analysed in a linear mixed model with period(trial), treatment*dose, treatment*sex , bodyweight as fixed effects and subject as a random effect.
One value of AUC(0-1h) was 0 and therefore excluded (NovoRapid 0.1 U/kg)

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:35 - a_pkpd_sex.sas/a_pd_sex_bw.txt

45: GIR AUC(0-30min) - treatment and sex ratios adjusted for bodyweight (75 kg) - adults, trials 3887,3891,3978

	N	Estimate	95% CI	P-value
AUCGIR(0-30min)(mg/kg)				
LSMeans				
Faster Aspart : Female	61	55.28		
Faster Aspart : Male	192	51.37		
NovoRapid : Female	49	24.97		
NovoRapid : Male	199	31.46		
Difference				
Faster Aspart-NovoRapid : Female		30.17	[17.85;42.48]	<0.001
Faster Aspart-NovoRapid : Male		19.76	[12.42;27.10]	<0.001
Female-Male : Faster Aspart		15.65	[-32.40;63.70]	0.522
Female-Male : NovoRapid		5.24	[-35.58;46.07]	0.801
Ratio				
Faster Aspart/NovoRapid - Female		2.21	[1.78;2.66]	
Faster Aspart/NovoRapid - Male		1.63	[1.45;1.90]	
Female/Male - Faster Aspart		1.08	[0.95;1.18]	
Female/Male - NovoRapid		0.79	[0.65;1.01]	
Treatment*Sex				
Interaction				0.157

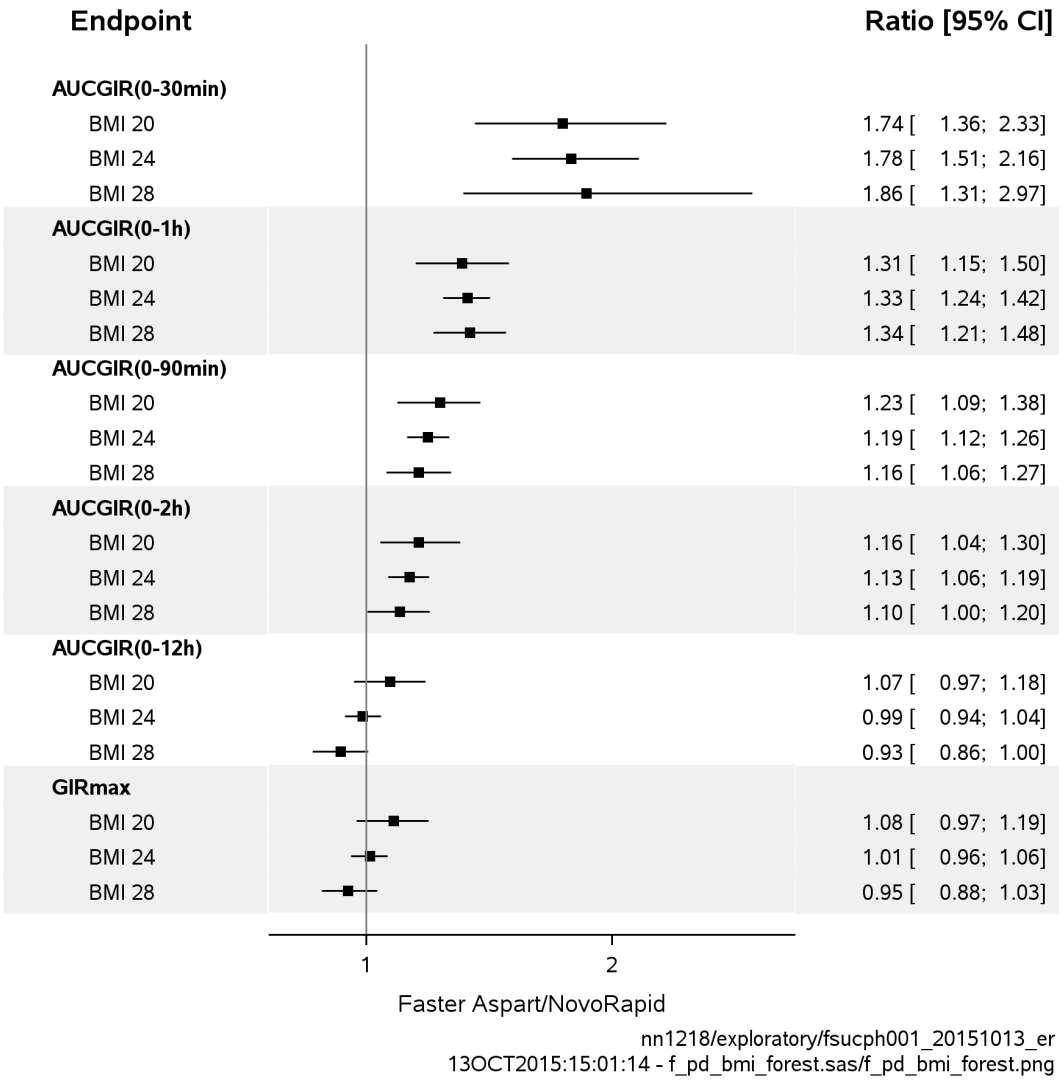
N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was analysed using a linear mixed model with
period(trial), treatment*dose, treatment*sex , bodyweight as fixed effects
and subject as a random effect and dose-dependent residual variance.
nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:21 - a_pd_sex_add_fi.sas/a_gir_sex_bw_add_fi.txt

46: GIR AUC(0-30min) - treatment and bmi ratios - adults, trials 3887,3891,3978

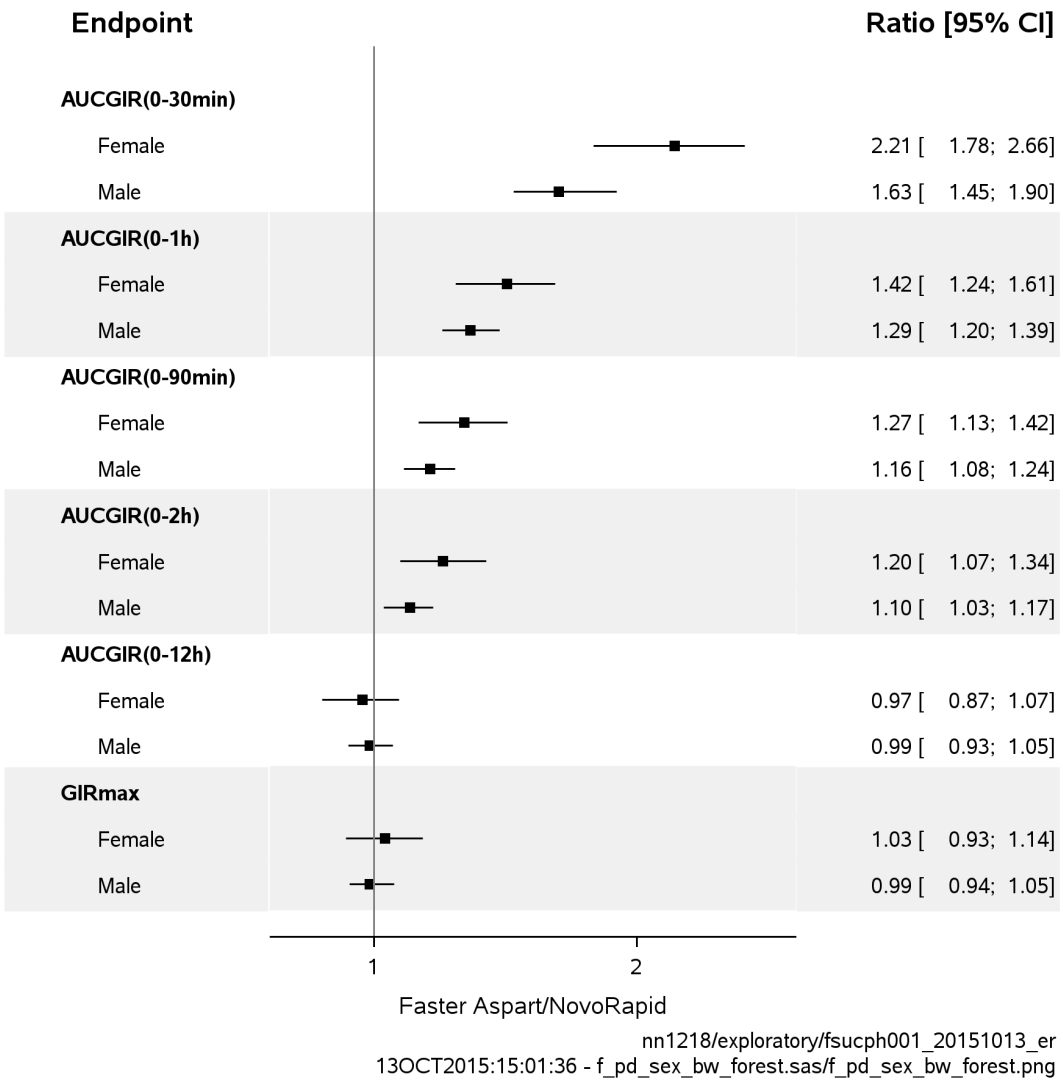
	N	Estimate	95% CI	P-value
AUCGIR(0-30min)(mg/kg)				
Faster Aspart	253			
NovoRapid	248			
Faster Aspart/NovoRapid - BMI 20		1.74	[1.36;2.33]	<0.001
Faster Aspart/NovoRapid - BMI 24		1.78	[1.51;2.16]	<0.001
Faster Aspart/NovoRapid - BMI 28		1.86	[1.31;2.97]	<0.001
BMI 20/BMI 24 : Faster Aspart		1.24	[1.10;1.38]	<0.001
BMI 20/BMI 24 : NovoRapid		1.28	[1.03;1.53]	0.032
BMI 20/BMI 28 : Faster Aspart		1.64	[1.23;2.22]	<0.001
BMI 20/BMI 28 : NovoRapid		1.76	[1.05;3.22]	0.032
BMI 24/BMI 28 : Faster Aspart		1.32	[1.11;1.61]	<0.001
BMI 24/BMI 28 : NovoRapid		1.38	[1.03;2.11]	0.032
Interaction BMI*treatment				0.314

N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was analysed using a linear mixed model with
period(trial), treatment*dose, treatment*BMI as fixed effects
and subject as a random effect and dose-dependent residual variance.

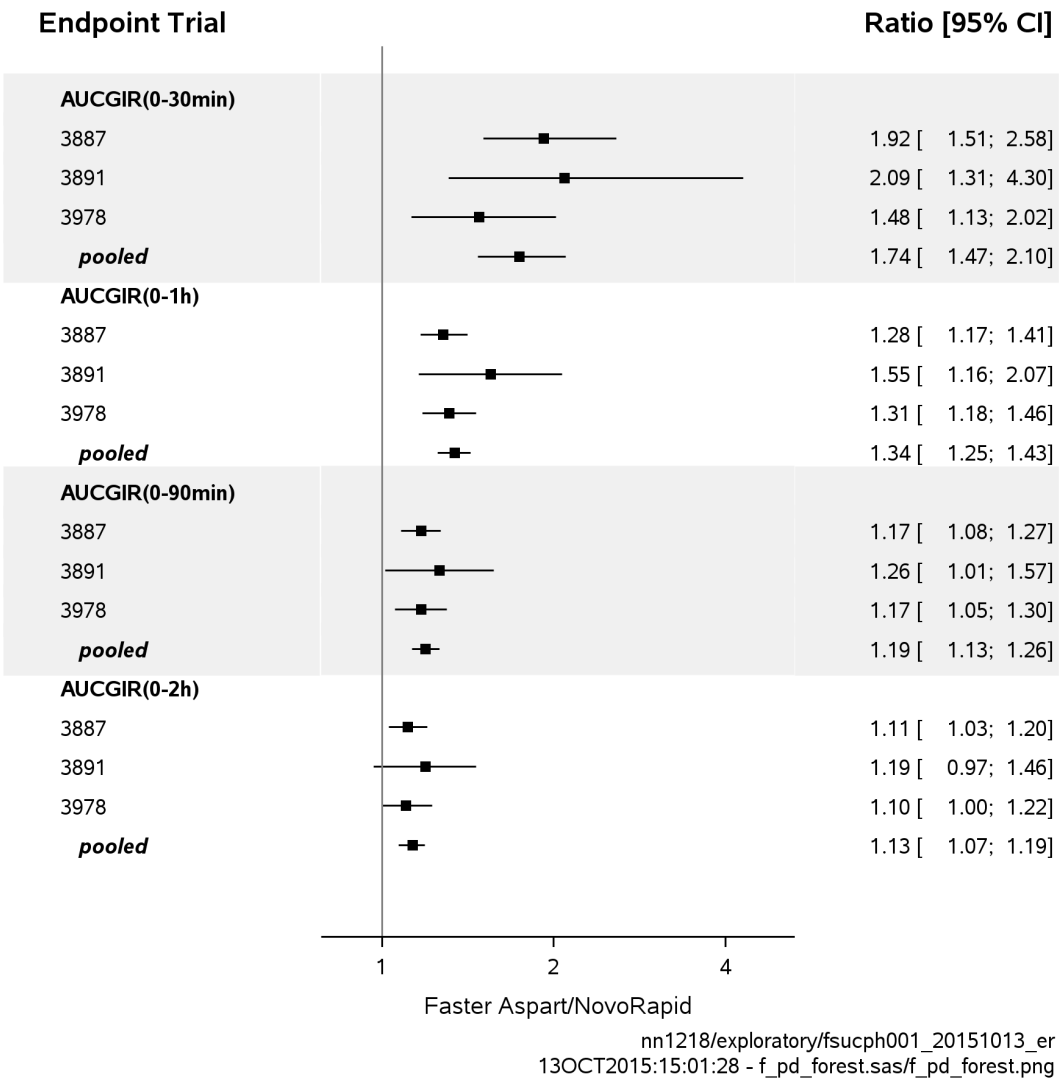
nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:04 - a_pd_bmi_add_fi.sas/a_gir_bmi_add_fi.txt



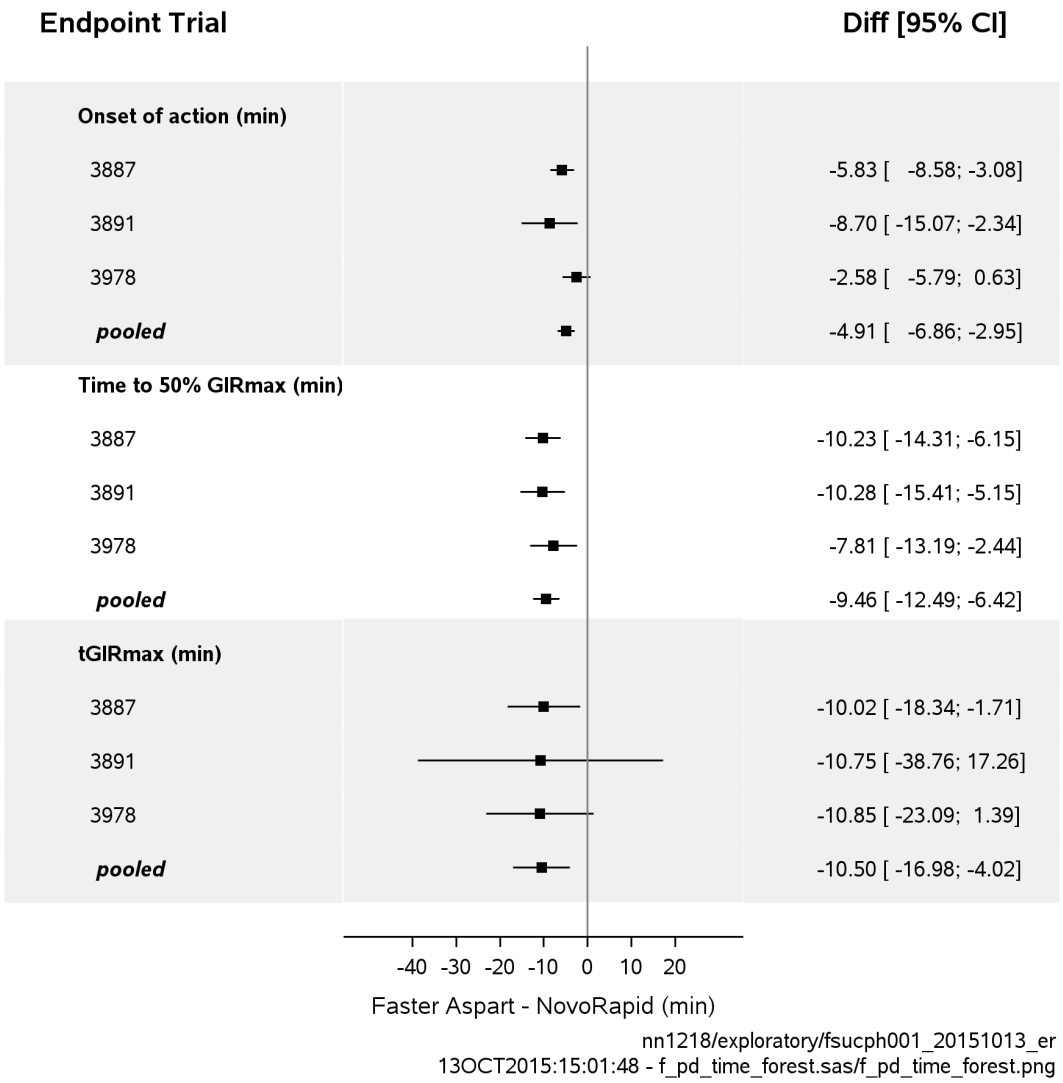
47: PD endpoints by BMI - treatment ratios - adults, trials 3887, 3891, 3978



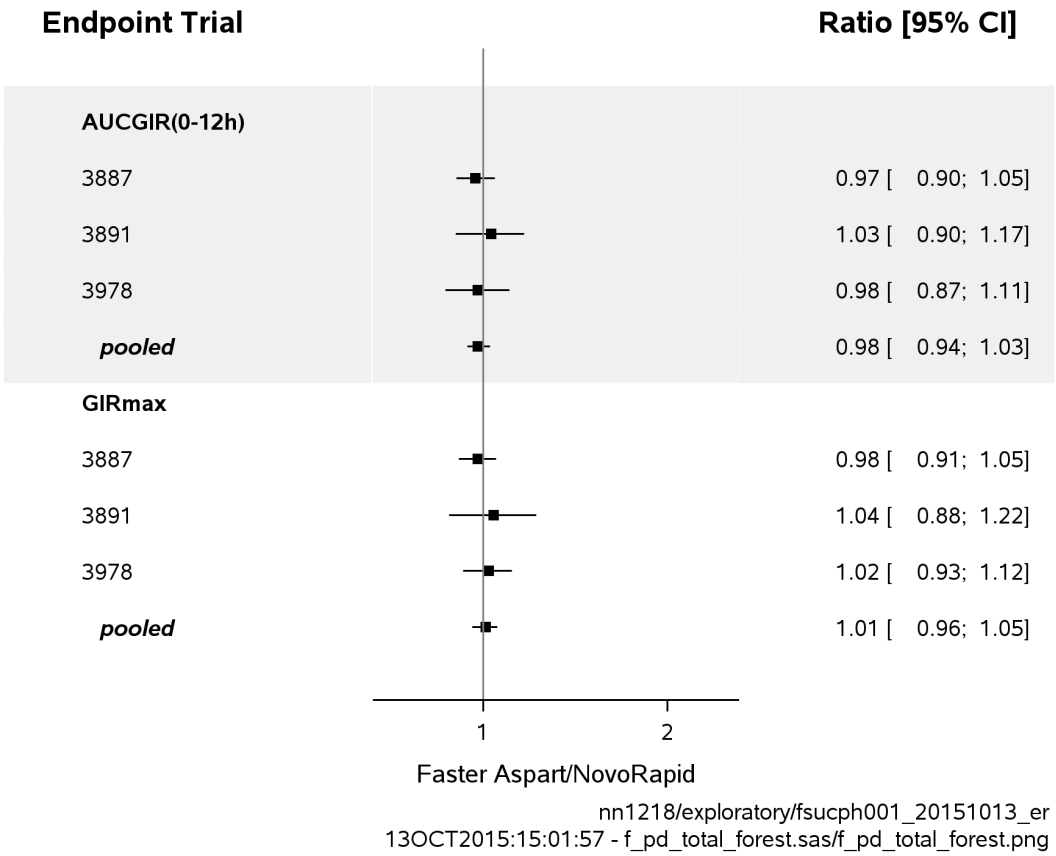
48: PD endpoints by sex adjusted for bodyweight (75kg) - treatment ratios - adults, trials 3887, 3891, 3978



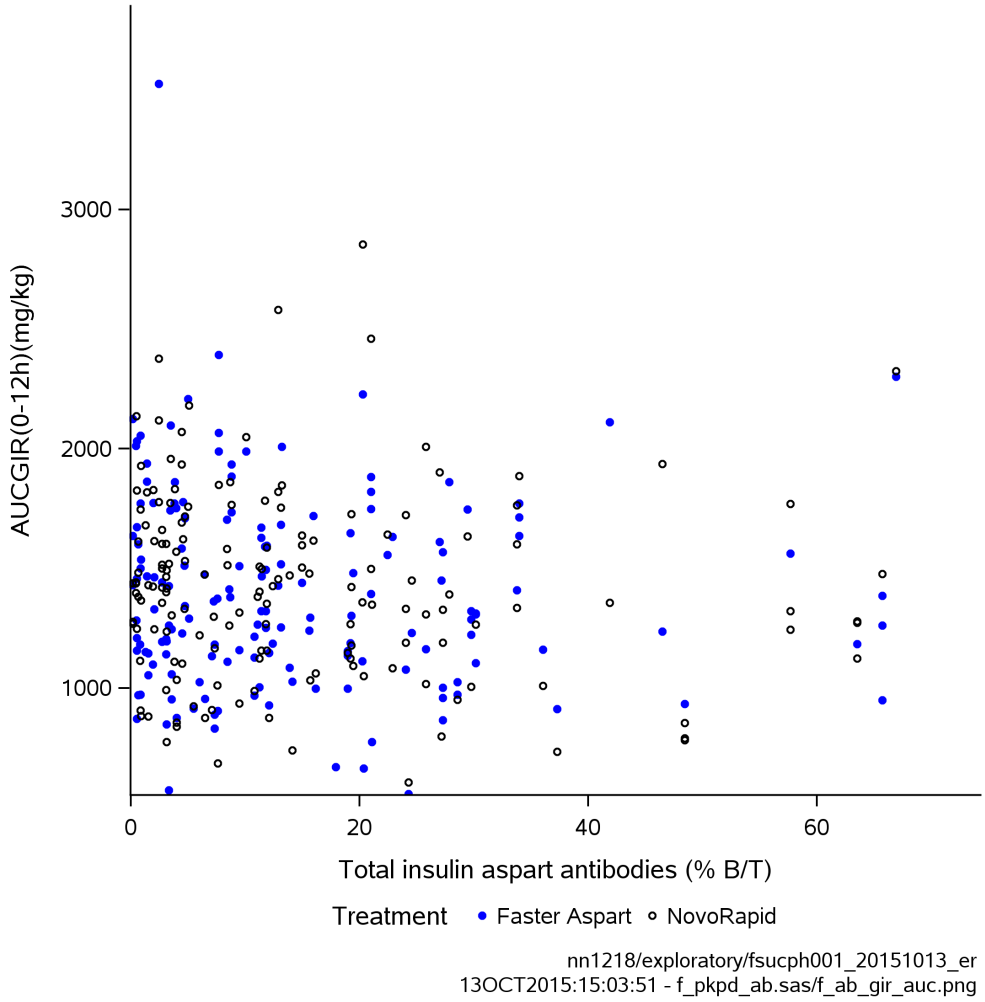
49: Early AUCGIR by trial - treatment ratios - adults, 0.2 U/kg, trials 3887, 3891, 3978



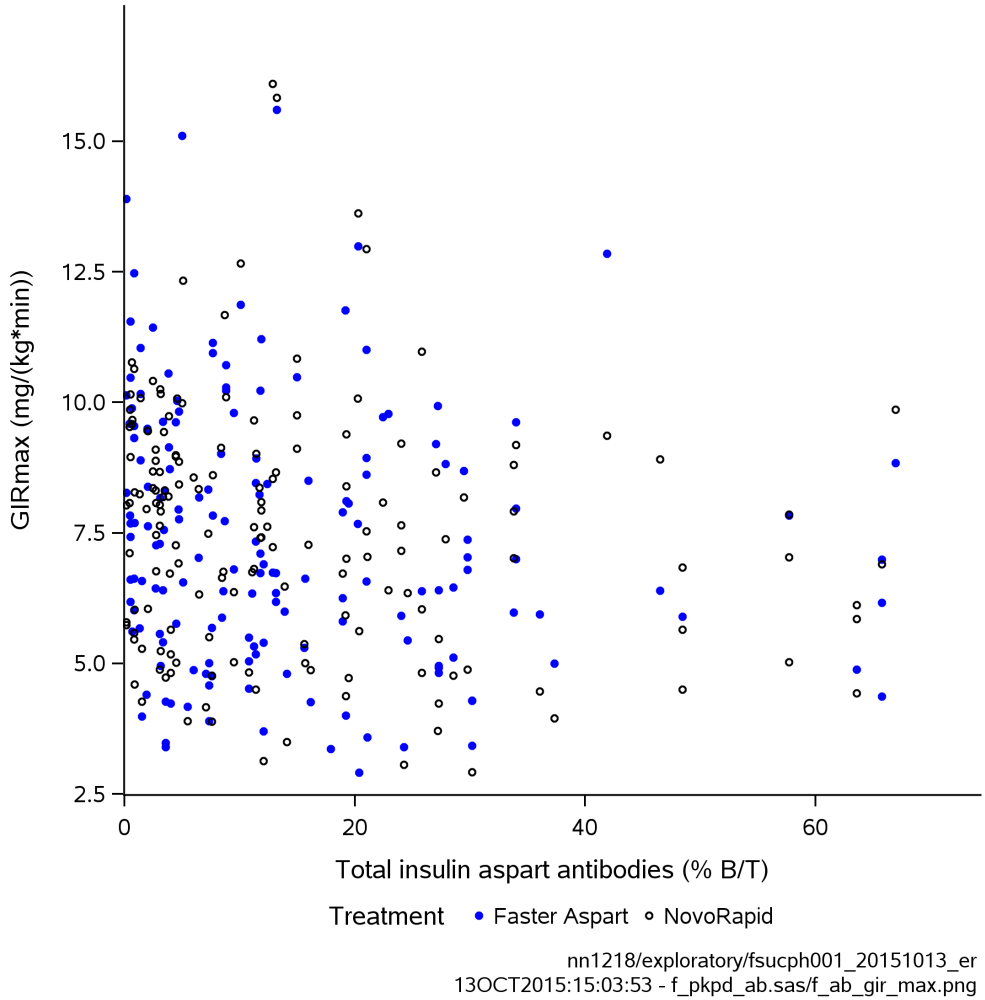
50: PD time parameters by trial - treatment differences - adults, 0.2 U/kg, trials 3887, 3891, 3978



51: AUCGIR(0-12h) and GIRmax by trial - treatment ratios - adults, 0.2 U/kg, trials 3887, 3891, 3978



52: AUCGIR(0-12h) vs antibodies - adults, 0.2 U/kg, trials 3887,3891,3978



53: GIRmax vs antibodies - adults, 0.2 U/kg, trials 3887,3891,3978

54: GIR endpoints vs total insulin antibodies - AUCGIR and GIRmax - statistical analysis - adjusted for dose level and bodyweight - adults, trials 3887,3891,3978

	N	Estimate	SE	95% CI	P-value
AUCGIR(0-1h)(mg/kg)					
Faster Aspart	253				
NovoRapid	247				
FA - ab 50th/25th percentile		0.9417	0.0236	[0.8987;0.9867]	0.012
FA - ab 75th/25th percentile		0.8801	0.0502	[0.7970;0.9719]	0.012
NR - ab 50th/25th percentile		0.9229	0.0235	[0.8810;0.9668]	<0.001
NR - ab 75th/25th percentile		0.8432	0.0499	[0.7640;0.9308]	<0.001
ab 25th percentile - FA/NR		1.2999	0.0365	[1.2099;1.3966]	<0.001
ab 50th percentile - FA/NR		1.3255	0.0339	[1.2400;1.4169]	<0.001
ab 75th percentile - FA/NR		1.3568	0.0413	[1.2510;1.4715]	<0.001
AUCGIR(0-12h)(mg/kg)					
Faster Aspart	253				
NovoRapid	248				
FA - ab 50th/25th percentile		0.9938	0.0171	[0.9608;1.0279]	0.716
FA - ab 75th/25th percentile		0.9869	0.0363	[0.9185;1.0603]	0.716
NR - ab 50th/25th percentile		0.9812	0.0170	[0.9488;1.0147]	0.266
NR - ab 75th/25th percentile		0.9605	0.0361	[0.8943;1.0316]	0.266
ab 25th percentile - FA/NR		0.9739	0.0280	[0.9217;1.0291]	0.347
ab 50th percentile - FA/NR		0.9860	0.0261	[0.9368;1.0379]	0.589
ab 75th percentile - FA/NR		1.0007	0.0317	[0.9402;1.0650]	0.983
GIRmax (mg/(kg*min))					
Faster Aspart	253				
NovoRapid	248				
FA - ab 50th/25th percentile		0.9809	0.0190	[0.9446;1.0185]	0.312
FA - ab 75th/25th percentile		0.9598	0.0404	[0.8860;1.0397]	0.312
NR - ab 50th/25th percentile		0.9551	0.0189	[0.9200;0.9916]	0.017
NR - ab 75th/25th percentile		0.9071	0.0403	[0.8376;0.9823]	0.017
ab 25th percentile - FA/NR		0.9813	0.0279	[0.9289;1.0367]	0.500
ab 50th percentile - FA/NR		1.0069	0.0260	[0.9568;1.0597]	0.791
ab 75th percentile - FA/NR		1.0384	0.0316	[0.9758;1.1049]	0.234

N: Number of profiles contributing to analysis.
SE: Standard error, CI: Confidence interval.
The log-transformed endpoint was analysed in a linear mixed model with dose(treatment) and period(trial) as fixed factors, log(bodyweight) and log(1+ab/13*) as covariates with treatment dependent slopes and subject(trial) as random effect.
Insulin antibody levels < 0 were set to 0.
*median from trial 3852 week 26

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:58 - a_pkpd_ab.sas/a_gir_ab.txt

55: Trial 3930: Descriptive statistics for meal test dose (U/kg) by treatment

Treatment	Median	Min	Max	N
Faster Aspart	0.145	0.084	0.359	39
NovoLog	0.157	0.073	0.370	35

N: Number of subjects

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:15:04:07 - t_3930_dose.sas/t_3930_dose.txt

56: IAsp Endpoints - additional AUCs- Statistical Analysis - trial 3978

	N	Estimate	SE	95% CI	P-value
AUC(0-90min) (pmol*h/L)					
LSMeans					
FIA (Q)	51	328.76	0.06		
NovoRapid	51	295.38	0.06		
Treatment Ratio					
FIA(Q) / NovoRapid		1.11		[1.01;1.22]	0.029
AUC(0-inf) (pmol*h/L)					
LSMeans					
FIA (Q)	51	757.35	0.05		
NovoRapid	51	787.73	0.05		
Treatment Ratio					
FIA(Q) / NovoRapid		0.96		[0.87;1.06]	0.428
AUC(2-12h)(h*pmol/L)					
LSMeans					
FIA (Q)	51	272.65	0.10		
NovoRapid	51	327.79	0.10		
Treatment Ratio					
FIA(Q) / NovoRapid		0.83		[0.68;1.02]	0.081

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error of the Mean
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:28 - a_pkpd_log_3978.sas/a_pk_log_extra_3978.txt

57: IAsp endpoints - onset of appearance, tmax, time to 50% cmax , time to late 50% cmax - statistical analysis - trial 3978

	N	Estimate	SE	95% CI	P-value
Onset of appearance (min)					
LSMeans					
FIA (Q)	51	3.59	0.35		
NovoRapid	51	8.87	0.35		
Treatment Difference					
FIA (Q) - NovoRapid		-5.28		[-6.07;-4.50]	<0.001
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.40		[0.33;0.48]	
tmax (min)					
LSMeans					
FIA (Q)	51	62.87	3.73		
NovoRapid	51	69.73	3.73		
Treatment Difference					
FIA (Q) - NovoRapid		-6.86		[-15.85;2.14]	0.134
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.90		[0.79;1.03]	
Time to 50% Cmax (min)					
LSMeans					
FIA (Q)	51	20.67	1.03		
NovoRapid	51	31.56	1.03		
Treatment Difference					
FIA (Q) - NovoRapid		-10.89		[-13.29;-8.50]	<0.001
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.65		[0.59;0.72]	
Time to late 50% Cmax					
LSMeans					
FIA (Q)	51	156.04	6.50		
NovoRapid	51	165.67	6.50		
Treatment Difference					
FIA (Q) - NovoRapid		-9.64		[-22.42;3.15]	0.138
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.94		[0.87;1.02]	

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error of the Mean
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:12 - a_pkpd_add_fi_3978.sas/a_pk_extra_ad_fi_3978.txt

58: PD endpoints - GIR AUC(2-12h) - statistical analysis - trial 3978

	N	Estimate	SE	95% CI	P-value
AUCGIR(2-12h)(mg/kg)					
LSMeans					
FIA (Q)	51	773.68	0.10		
NovoRapid	51	873.15	0.10		
Treatment Ratio					
FIA(Q) / NovoRapid		0.89		[0.68;1.16]	0.379

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error of the Mean
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:28 - a_pkpd_log_3978.sas/a_gir_log_extra_3978.txt

59: PD endpoints - time to 50% GIRmax, tGIRmax, time to late 50% GIRmax - statistical analysis - trial 3978

	N	Estimate	SE	95% CI	P-value
tGIRmax (min)					
LSMeans					
FIA (Q)	51	124.31	5.87		
NovoRapid	51	135.16	5.87		
Treatment Difference					
FIA (Q) - NovoRapid		-10.85		[-23.09;1.39]	0.082
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.92		[0.84;1.01]	
Time to 50% GIRmax (min)					
LSMeans					
FIA (Q)	51	38.25	2.22		
NovoRapid	51	46.06	2.22		
Treatment Difference					
FIA (Q) - NovoRapid		-7.81		[-13.19;-2.44]	0.005
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.83		[0.73;0.94]	
Time to late 50% GIRmax					
LSMeans					
FIA (Q)	51	233.48	9.02		
NovoRapid	51	246.80	9.02		
Treatment Difference					
FIA (Q) - NovoRapid		-13.32		[-36.33;9.69]	0.253
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.95		[0.86;1.04]	

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error of the Mean
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:12 - a_pkpd_add_fi_3978.sas/a_gir_extra_ad_fi_3978.txt

60: BG endpoint - onset of action - Statistical Analysis - trial 3978

	N	Estimate	SE	95% CI	P-value
Onset of action (min)					
LSMeans					
FIA (Q)	51	13.42	1.20		
NovoRapid	51	16.00	1.20		
Treatment Difference					
FIA (Q) - NovoRapid		-2.58		[-5.79;0.63]	0.114
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.84		[0.67;1.04]	

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error of the Mean
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:13 - a_pkpd_add_fi_3978.sas/a_bg_extra_ad_fi_3978.txt

61: Insulin Aspart endpoint - AUC(2-12h) - statistical analysis - trial 3891 full analysis set

	N	Estimate	95% CI	P-value
Secondary endpoint:				
AUC(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart : Geriatric	29	304.40		
Faster Aspart : Younger	37	249.67		
NovoRapid : Geriatric	30	339.34		
NovoRapid : Younger	36	223.88		
Age group/Treatment ratio				
Faster Aspart : Geriatric/Younger		1.22	[0.83;1.78]	
NovoRapid : Geriatric/Younger		1.52	[1.04;2.22]	
Geriatric : Faster Aspart/NovoRapid		0.90	[0.78;1.03]	
Younger : Faster Aspart/NovoRapid		1.12	[0.79;1.58]	
Age by treatment interaction				0.244

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and residual variance depends on age group.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:24 - a_pkpd_log_3891.sas/a_pk_extra_log_3891.txt

62: Insulin Aspart endpoint - AUC(2-12h) - sensitivity analysis - trial 3891

	N	Estimate	95% CI	P-value
Secondary endpoint:				
AUC(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart : Geriatric	29	304.43		
Faster Aspart : Younger	36	251.46		
NovoRapid : Geriatric	30	339.32		
NovoRapid : Younger	35	264.75		
Age group/Treatment ratio				
Faster Aspart : Geriatric/Younger		1.21	[0.89;1.65]	
NovoRapid : Geriatric/Younger		1.28	[0.94;1.74]	
Geriatric : Faster Aspart/NovoRapid		0.90	[0.78;1.03]	
Younger : Faster Aspart/NovoRapid		0.95	[0.82;1.10]	
Age by treatment interaction				0.557

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and residual variance depends on age group.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:25 - a_pkpd_log_3891.sas/a_pk_extra_log_3891_sens.txt

63: Insulin Aspart endpoints - time to late 50% Cmax and tmax - statistical analysis - trial 3891 full analysis set

	N	Estimate	95% CI	P-value
tmax (min)				
LSMeans				
Faster Aspart : Geriatric	29	57.16		
Faster Aspart : Younger	37	54.22		
NovoRapid : Geriatric	30	64.16		
NovoRapid : Younger	36	59.05		
Age group/Treatment difference				
Faster Aspart : Geriatric - Younger		2.94	[-9.17;15.06]	
NovoRapid : Geriatric - Younger		5.11	[-6.96;17.18]	
Geriatric : Faster Aspart - NovoRapid		-7.00	[-17.59;3.60]	
Younger : Faster Aspart - NovoRapid		-4.83	[-14.59;4.93]	
Age by treatment interaction				0.760
Fieller age group/treatment ratio				
Faster Aspart : Geriatric/Younger		1.05	[0.84;1.31]	
NovoRapid : Geriatric/Younger		1.09	[0.89;1.32]	
Geriatric : Faster Aspart/NovoRapid		0.89	[0.75;1.06]	
Younger : Faster Aspart/NovoRapid		0.92	[0.77;1.09]	
Time to late 50% Cmax				
LSMeans				
Faster Aspart : Geriatric	29	148.55		
Faster Aspart : Younger	37	142.08		
NovoRapid : Geriatric	30	159.91		
NovoRapid : Younger	36	147.20		
Age group/Treatment difference				
Faster Aspart : Geriatric - Younger		6.47	[-15.73;28.67]	
NovoRapid : Geriatric - Younger		12.71	[-9.49;34.90]	
Geriatric : Faster Aspart - NovoRapid		-11.36	[-24.49;1.77]	
Younger : Faster Aspart - NovoRapid		-5.12	[-20.62;10.38]	
Age by treatment interaction				0.533
Fieller age group/treatment ratio				
Faster Aspart : Geriatric/Younger		1.05	[0.89;1.22]	
NovoRapid : Geriatric/Younger		1.09	[0.94;1.26]	
Geriatric : Faster Aspart/NovoRapid		0.93	[0.85;1.01]	
Younger : Faster Aspart/NovoRapid		0.97	[0.87;1.07]	

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was analysed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect.
The variance of the random effect and residual variance depends on age group.
Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:09 - a_pkpd_add_fi_3891.sas/a_pk_extra_add_fi_3891.txt

64: Insulin Aspart endpoint - time to late 50% Cmax - sensitivity analysis - trial 3891

	N	Estimate	95% CI	P-value
Time to late 50% Cmax				
LSMeans				
Faster Aspart : Geriatric	29	148.49		
Faster Aspart : Younger	36	143.90		
NovoRapid : Geriatric	30	159.96		
NovoRapid : Younger	35	150.46		
Age group/Treatment difference				
Faster Aspart : Geriatric - Younger		4.60	[-17.20;26.39]	
NovoRapid : Geriatric - Younger		9.50	[-12.29;31.30]	
Geriatric : Faster Aspart - NovoRapid		-11.46	[-24.56;1.63]	
Younger : Faster Aspart - NovoRapid		-6.56	[-22.25;9.13]	
Age by treatment interaction				0.626
Fieller age group/treatment ratio				
Faster Aspart : Geriatric/Younger		1.03	[0.88;1.20]	
NovoRapid : Geriatric/Younger		1.06	[0.92;1.23]	
Geriatric : Faster Aspart/NovoRapid		0.93	[0.85;1.01]	
Younger : Faster Aspart/NovoRapid		0.96	[0.86;1.06]	

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was analysed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect.
The variance of the random effect and residual variance depends on age group.
Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:09 - a_pkpd_add_fi_3891.sas/a_pk_add_fi_3891_sens.txt

65: GIR endpoint - AUCGIR(2-12h) - statistical analysis - trial 3891 full analysis set

	N	Estimate	95% CI	P-value
Secondary endpoint:				
AUCGIR(2-12h)(mg/kg)				
LSMeans				
Faster Aspart : Geriatric	21	664.86		
Faster Aspart : Younger	22	664.78		
NovoRapid : Geriatric	22	626.92		
NovoRapid : Younger	21	717.54		
Age group/Treatment ratio				
Faster Aspart : Geriatric/Younger		1.00	[0.76;1.32]	
NovoRapid : Geriatric/Younger		0.87	[0.66;1.15]	
Geriatric : Faster Aspart/NovoRapid		1.06	[0.85;1.32]	
Younger : Faster Aspart/NovoRapid		0.93	[0.81;1.06]	
Age by treatment interaction				0.284

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect. The variance of the random effect and residual variance depends on age group.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:26 - a_pkpd_log_3891.sas/a_pd_extra_log_3891.txt

66: GIR endpoints - time to GIRmax and late 50% GIRmax - statistical analysis - trial 3891 full analysis set

	N	Estimate	95% CI	P-value
tGIRmax (min)				
LSMeans				
Faster Aspart : Geriatric	21	136.23		
Faster Aspart : Younger	22	113.84		
NovoRapid : Geriatric	22	145.83		
NovoRapid : Younger	21	124.59		
Age group/Treatment difference				
Faster Aspart : Geriatric - Younger		22.39	[-5.59;50.37]	
NovoRapid : Geriatric - Younger		21.24	[-6.72;49.19]	
Geriatric : Faster Aspart - NovoRapid		-9.59	[-33.65;14.46]	
Younger : Faster Aspart - NovoRapid		-10.75	[-38.76;17.26]	
Age by treatment interaction				0.948
Fieller age group/treatment ratio				
Faster Aspart : Geriatric/Younger		1.20	[0.95;1.51]	
NovoRapid : Geriatric/Younger		1.17	[0.95;1.45]	
Geriatric : Faster Aspart/NovoRapid		0.93	[0.79;1.10]	
Younger : Faster Aspart/NovoRapid		0.91	[0.72;1.15]	
Time to late 50% GIRmax				
LSMeans				
Faster Aspart : Geriatric	21	247.38		
Faster Aspart : Younger	22	219.15		
NovoRapid : Geriatric	22	257.59		
NovoRapid : Younger	21	239.31		
Age group/Treatment difference				
Faster Aspart : Geriatric - Younger		28.23	[-0.90;57.36]	
NovoRapid : Geriatric - Younger		18.28	[-10.81;47.37]	
Geriatric : Faster Aspart - NovoRapid		-10.20	[-31.37;10.96]	
Younger : Faster Aspart - NovoRapid		-20.15	[-41.95;1.65]	
Age by treatment interaction				0.498
Fieller age group/treatment ratio				
Faster Aspart : Geriatric/Younger		1.13	[0.99;1.28]	
NovoRapid : Geriatric/Younger		1.08	[0.95;1.21]	
Geriatric : Faster Aspart/NovoRapid		0.96	[0.88;1.04]	
Younger : Faster Aspart/NovoRapid		0.92	[0.83;1.00]	

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was analysed using a linear mixed model with age group, treatment, age group by treatment interaction and period as fixed effects and subject as a random effect.
The variance of the random effect and residual variance depends on age group.
Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:10 - a_pkpd_add_fi_3891.sas/a_pd_extra_add_fi_3891.txt

67: IAsp endpoints - AUC(0-12h), AUC(2-12h) - statistical analysis - trial 3887

	N	Estimate	95% CI	P-value
AUC(0-12h) (pmol*h/L)				
LSMeans				
Faster Aspart 0.1 U/kg	45	303.12		
Faster Aspart 0.2 U/kg	91	727.41		
Faster Aspart 0.4 U/kg	45	1614.55		
NovoRapid 0.1 U/kg	44	330.43		
NovoRapid 0.2 U/kg	88	703.77		
NovoRapid 0.4 U/kg	44	1737.12		
Treatment ratio				
0.1 U/kg : Faster Aspart/NovoRapid		0.92	[0.85;0.99]	0.021
0.2 U/kg : Faster Aspart/NovoRapid		1.03	[0.98;1.09]	0.237
0.4 U/kg : Faster Aspart/NovoRapid		0.93	[0.86;1.00]	0.050
AUC(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart 0.1 U/kg	45	100.17		
Faster Aspart 0.2 U/kg	91	260.52		
Faster Aspart 0.4 U/kg	45	608.74		
NovoRapid 0.1 U/kg	44	113.94		
NovoRapid 0.2 U/kg	88	286.02		
NovoRapid 0.4 U/kg	44	789.91		
Treatment ratio				
0.1 U/kg : Faster Aspart/NovoRapid		0.88	[0.78;0.99]	0.032
0.2 U/kg : Faster Aspart/NovoRapid		0.91	[0.83;0.99]	0.038
0.4 U/kg : Faster Aspart/NovoRapid		0.77	[0.69;0.87]	<0.001

N: Number of profiles contributing to analysis, CI: Confidence interval,
The endpoint was log-transformed and analysed using a linear mixed model with period, treatment, dose and dose by treatment interaction as fixed effects and subject as a random effect.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:21 - a_pkpd_log_3887.sas/a_pk_extra_log_3887.txt

68: IAsp endpoint - time to late 50% Cmax - statistical analysis - trial 3887 full analysis set

	N	Estimate	95% CI	P-value
Time to late 50% Cmax				
LSMeans				
Faster Aspart 0.1 U/kg	45	144.11		
Faster Aspart 0.2 U/kg	91	150.03		
Faster Aspart 0.4 U/kg	45	156.76		
NovoRapid 0.1 U/kg	44	148.07		
NovoRapid 0.2 U/kg	88	170.15		
NovoRapid 0.4 U/kg	44	176.52		
Treatment difference				
0.1 U/kg : Faster Aspart-NovoRapid		-3.96	[-15.62;7.69]	0.496
0.2 U/kg : Faster Aspart-NovoRapid		-20.12	[-32.07;-8.17]	0.001
0.4 U/kg : Faster Aspart-NovoRapid		-19.76	[-33.22;-6.30]	0.005
Treatment ratio				
0.1 U/kg : Faster Aspart/NovoRapid		0.97	[0.90;1.05]	
0.2 U/kg : Faster Aspart/NovoRapid		0.88	[0.82;0.95]	
0.4 U/kg : Faster Aspart/NovoRapid		0.89	[0.82;0.96]	

N: Number of profiles contributing to analysis, CI: Confidence interval
The endpoint was analysed using a linear mixed model with period, treatment, dose and dose by treatment interaction as fixed effects and subject and the interaction between subject and dose as random effects. The between- and within-subject variances depend on dose.
Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:05 - a_pkpd_add_fi_3887.sas/a_pk_extra_ad_fi_3887.txt

69: PD endpoints - GIR AUC(0-12h), GIR AUC(2-12h) - statistical analysis - trial 3887

	N	Estimate	95% CI	P-value
Primary endpoint:				
AUCGIR(0-12h) (mg/kg)				
LSMeans				
Faster Aspart 0.1 U/kg	45	646.77		
Faster Aspart 0.2 U/kg	90	1352.76		
Faster Aspart 0.4 U/kg	45	2338.74		
NovoRapid 0.1 U/kg	44	656.11		
NovoRapid 0.2 U/kg	88	1391.06		
NovoRapid 0.4 U/kg	44	2410.20		
Treatment ratio				
0.1 U/kg : Faster Aspart/NovoRapid		0.99	[0.89;1.09]	0.773
0.2 U/kg : Faster Aspart/NovoRapid		0.97	[0.90;1.05]	0.451
0.4 U/kg : Faster Aspart/NovoRapid		0.97	[0.88;1.07]	0.544
Secondary endpoint:				
AUCGIR(2-12h)(mg/kg)				
LSMeans				
Faster Aspart 0.1 U/kg	45	276.96		
Faster Aspart 0.2 U/kg	90	754.94		
Faster Aspart 0.4 U/kg	45	1468.16		
NovoRapid 0.1 U/kg	44	314.29		
NovoRapid 0.2 U/kg	88	840.53		
NovoRapid 0.4 U/kg	44	1680.45		
Treatment ratio				
0.1 U/kg : Faster Aspart/NovoRapid		0.88	[0.77;1.01]	0.064
0.2 U/kg : Faster Aspart/NovoRapid		0.90	[0.81;0.99]	0.035
0.4 U/kg : Faster Aspart/NovoRapid		0.87	[0.76;1.00]	0.047

N: Number of profiles contributing to analysis, CI: Confidence interval,
The endpoint was log-transformed and analysed using a linear mixed model with period, treatment, dose and dose by treatment interaction as fixed effects and subject as a random effect.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:21 - a_pkpd_log_3887.sas/a_gir_extra_log_3887.txt

70: GIR endpoint - time to late 50% GIRmax - statistical analysis - trial 3887 full analysis set

	N	Estimate	95% CI	P-value
Time to late 50% GIRmax				
LSMeans				
Faster Aspart 0.1 U/kg	45	191.13		
Faster Aspart 0.2 U/kg	90	230.59		
Faster Aspart 0.4 U/kg	45	275.32		
NovoRapid 0.1 U/kg	44	208.90		
NovoRapid 0.2 U/kg	88	243.19		
NovoRapid 0.4 U/kg	44	296.01		
Treatment difference				
0.1 U/kg : Faster Aspart-NovoRapid		-17.78	[-36.93;1.38]	0.068
0.2 U/kg : Faster Aspart-NovoRapid		-12.60	[-23.78;-1.42]	0.027
0.4 U/kg : Faster Aspart-NovoRapid		-20.69	[-35.02;-6.36]	0.006
Treatment ratio				
0.1 U/kg : Faster Aspart/NovoRapid		0.91	[0.83;1.01]	
0.2 U/kg : Faster Aspart/NovoRapid		0.95	[0.90;0.99]	
0.4 U/kg : Faster Aspart/NovoRapid		0.93	[0.88;0.98]	

N: Number of profiles contributing to analysis, CI: Confidence interval
The endpoint was analysed using a linear mixed model with period, treatment, dose and dose by treatment interaction as fixed effects and subject and the interaction between subject and dose as random effects. The between- and within-subject variances depend on dose.
Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:07 - a_pkpd_add_fi_3887.sas/a_gir_extra_ad_fi_3887.txt

71: IAsp endpoint - AUC(2-12h) - statistical analysis - trial 3888 - FAS

	N	Estimate	95% CI	P-value
Secondary endpoint:				
AUC(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart : Children	12	102.60		
Faster Aspart : Adolescents	13	159.01		
Faster Aspart : Adults	15	269.80		
NovoRapid : Children	12	119.52		
NovoRapid : Adolescents	13	169.54		
NovoRapid : Adults	13	317.77		
Age group/Treatment ratio				
Children : Faster Aspart/NovoRapid		0.86	[0.66;1.12]	
Adolescents : Faster Aspart/NovoRapid		0.94	[0.69;1.28]	
Adults : Faster Aspart/NovoRapid		0.85	[0.76;0.95]	
Faster Aspart : Children/Adults		0.38	[0.25;0.57]	
Faster Aspart : Adolescents/Adults		0.59	[0.41;0.84]	
NovoRapid : Children/Adults		0.38	[0.25;0.57]	
NovoRapid : Adolescents/Adults		0.53	[0.37;0.76]	
Age by treatment interaction				0.817

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:37 - a_pk_log_3888.sas/a_pk_log_3888.txt

72: Insulin Aspart endpoints - tmax and time to late 50% Cmax - statistical analysis - trial 3888 full analysis set

	N	Estimate	95% CI	P-value
tmax (min)				
LSMeans				
Faster Aspart : Children	12	48.46		
Faster Aspart : Adolescents	13	53.47		
Faster Aspart : Adults	15	59.27		
NovoRapid : Children	12	53.29		
NovoRapid : Adolescents	13	62.90		
NovoRapid : Adults	13	74.96		
Age group/Treatment difference				
Children : Faster Aspart - NovoRapid		-4.83	[-14.72;5.06]	
Adolescents : Faster Aspart - NovoRapid		-9.43	[-20.69;1.84]	
Adults : Faster Aspart - NovoRapid		-15.69	[-29.51;-1.88]	
Faster Aspart : Children - Adults		-10.82	[-28.37;6.74]	
Faster Aspart : Adolescents - Adults		-5.80	[-20.97;9.37]	
NovoRapid : Children - Adults		-21.68	[-39.75;-3.60]	
NovoRapid : Adolescents - Adults		-12.07	[-27.86;3.73]	
Age by treatment interaction				0.395
Fieller Treatment Ratio				
Children : Faster Aspart / NovoRapid	12	0.91	[0.74;1.10]	
Adolescents: Faster Aspart / NovoRapid	13	0.85	[0.70;1.02]	
Adults : Faster Aspart / NovoRapid	15	0.79	[0.64;0.96]	
Time to late 50% Cmax				
LSMeans				
Faster Aspart : Children	12	103.18		
Faster Aspart : Adolescents	13	128.15		
Faster Aspart : Adults	15	160.84		
NovoRapid : Children	12	113.46		
NovoRapid : Adolescents	13	139.39		
NovoRapid : Adults	13	163.80		
Age group/Treatment difference				
Children : Faster Aspart - NovoRapid		-10.28	[-30.37;9.81]	
Adolescents : Faster Aspart - NovoRapid		-11.24	[-33.15;10.67]	
Adults : Faster Aspart - NovoRapid		-2.96	[-19.59;13.68]	
Faster Aspart : Children - Adults		-57.66	[-89.81;-25.51	
Faster Aspart : Adolescents - Adults		-32.69	[-63.84;-1.54]	
NovoRapid : Children - Adults		-50.34	[-82.93;-17.74	
NovoRapid : Adolescents - Adults		-24.41	[-56.03;7.22]	
Age by treatment interaction				0.755
Fieller Treatment Ratio				
Children : Faster Aspart / NovoRapid	12	0.91	[0.76;1.09]	
Adolescents: Faster Aspart / NovoRapid	13	0.92	[0.78;1.08]	
Adults : Faster Aspart / NovoRapid	15	0.98	[0.89;1.09]	

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:02 - a_pkpd_ad_fi_3888.sas/a_pk_add_fi_3888.txt

73: Insulin Aspart endpoint - AUC(2-12h) - statistical analysis - trial 3889 full analysis set

	N	Estimate	95% CI	P-value
AUC(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart	35	183.25		
NovoRapid	36	202.88		
Treatment Ratio				
Faster Aspart / NovoRapid		0.90	[0.79;1.04]	0.145

N: Number of subjects contributing to analysis, CI: Confidence Interval
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:39 - a_pk_log_3889.sas/a_pk_extra_log_3889.txt

74: Insulin Aspart endpoint - time to late 50% Cmax - statistical analysis - trial 3889 full analysis set

	N	Estimate	SE	95% CI	P-value
Time to late 50% Cmax					
LSMeans					
Faster Aspart	35	140.45	7.08		
NovoRapid	36	147.93	7.03		
Treatment Difference					
Faster Aspart - NovoRapid		-7.48		[-18.65;3.69]	0.182
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.95		[0.88;1.03]	

N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error of mean
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:30 - a_pk_add_fi_3889.sas/a_pk_extra_add_fi_3889.txt

75: Insulin Aspart endpoint - AUC(2-12h) - statistical analysis - trial 3921 FAS

	N	Estimate	95% CI	P-value
AUC(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart	31	193.98		
NovoRapid	32	215.04		
Treatment Ratio				
Faster Aspart / NovoRapid		0.90	[0.78;1.05]	0.170

N: Number of subjects contributing to analysis; CI: Confidence Interval.
The endpoint was log-transformed and analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:42 - a_pk_log_3921.sas/a_pk_extra_log_3921.txt

76: Insulin Aspart endpoint - time to late 50% Cmax - statistical analysis - trial 3921 FAS

	N	Estimate	SE	95% CI	P-value
Time to late 50% Cmax					
LSMeans					
Faster Aspart	32	143.71	7.66		
NovoRapid	32	154.88	7.66		
Treatment Difference					
Faster Aspart - NovoRapid		-11.17		[-24.12;1.79]	0.088
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.93		[0.85;1.01]	

N: Number of subjects contributing to analysis; CI: Confidence interval; SE: Standard error of mean. The endpoint was analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:28 - a_pk_add_3921.sas/a_pk_extra_add_fi_3921.txt

77: IAsp endpoints - basal-insulin adjusted time to late 50 % Cmax - statistical analysis - additive model - trial 3890

	N	Estimate	SE	95% CI	P-value
Time to late 50% Cmax					
LSMeans					
Faster Aspart	44	137.45	6.50		
NovoRapid	46	172.86	6.41		
Treatment Difference					
Faster Aspart - NovoRapid		-35.42		[-47.02;-23.82]	<0.001
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.80		[0.73;0.86]	

N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error of mean The endpoint was analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:27 - a_pk_add_3890.sas/a_pk_add_time_3890.txt

78: IAsp endpoints - basal-insulin adjusted AUCs - statistical analysis - multiplicative model - trial 3890

	N	Estimate	95% CI	P-value
Secondary endpoints:				
AUC(2h-12h) (pmol*h/L)				
LSMeans				
Faster Aspart	44	212.58		
NovoRapid	46	277.07		
Treatment Ratio				
Faster Aspart / NovoRapid		0.77	[0.61;0.96]	0.022

N: Number of subjects contributing to analysis, CI: Confidence Interval
The endpoint was log-transformed and analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:41 - a_pk_log_3890.sas/a_pk_log_3890.txt

79: PD endpoints - basal-insulin adjusted time to late 50 % GIRmax - statistical analysis - additive model - trial 3890

	N	Estimate	SE	95% CI	P-value
Time to late 50% GIRmax					
LSMeans					
Faster Aspart	44	214.71	6.26		
NovoRapid	45	238.71	6.19		
Treatment Difference					
Faster Aspart - NovoRapid		-24.00		[-38.88;-9.13]	0.002
Fieller Treatment Ratio					
Faster Aspart/NovoRapid		0.90		[0.84;0.96]	

N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error of mean
The endpoint was analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:56:48 - a_pd_add_3890.sas/a_pd_add_time_3890.txt

80: PD endpoints - basal-insulin adjusted GIR AUCs - statistical analysis - multiplicative model - trial 3890

	N	Estimate	95% CI	P-value
AUC(2h-12h) (mg/kg)				
LSMeans				
Faster Aspart	44	774.67		
NovoRapid	45	805.53		
Treatment Ratio				
Faster Aspart / NovoRapid		0.96	[0.86;1.07]	0.480

N: Number of subjects contributing to analysis, CI: Confidence Interval
The endpoint was log-transformed and analysed in a linear mixed model with treatment and period as fixed effects and subject as a random effect

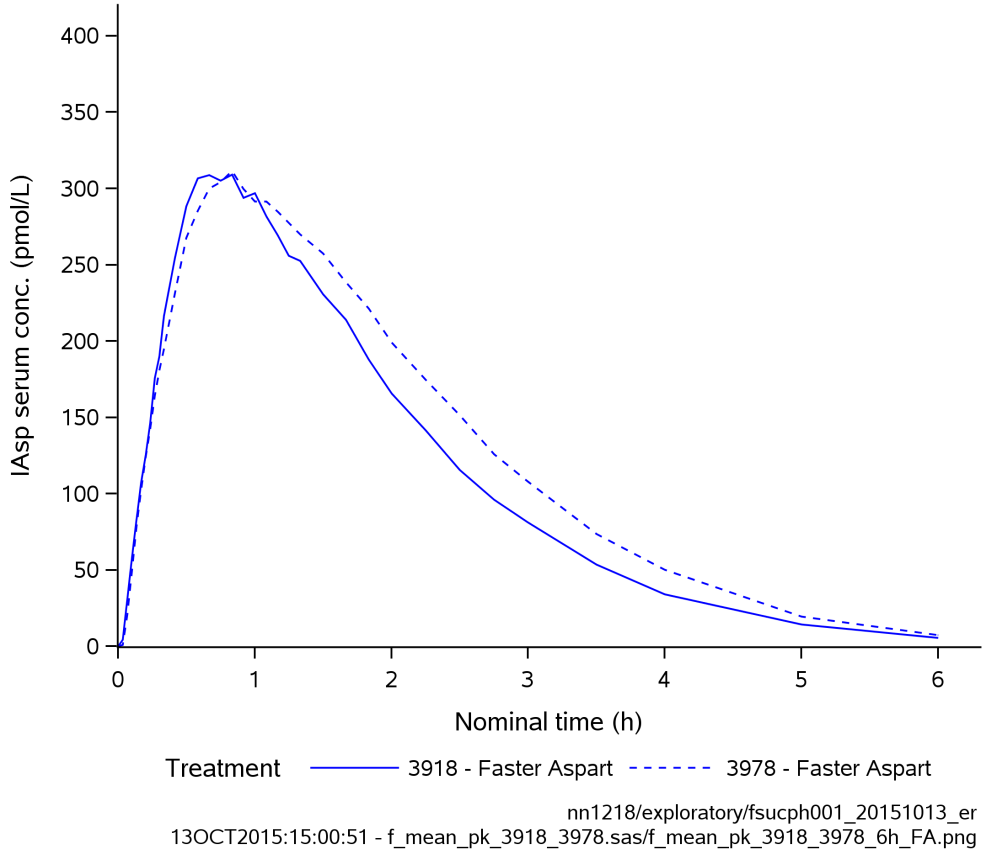
nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:57:07 - a_pd_log_3890.sas/a_pd_log_3890.txt

81: GIR endpoints - AUCGIR(0-1h) - within-subject variability - statistical analysis - 0.2 U/kg trial 3887 - full analysis set

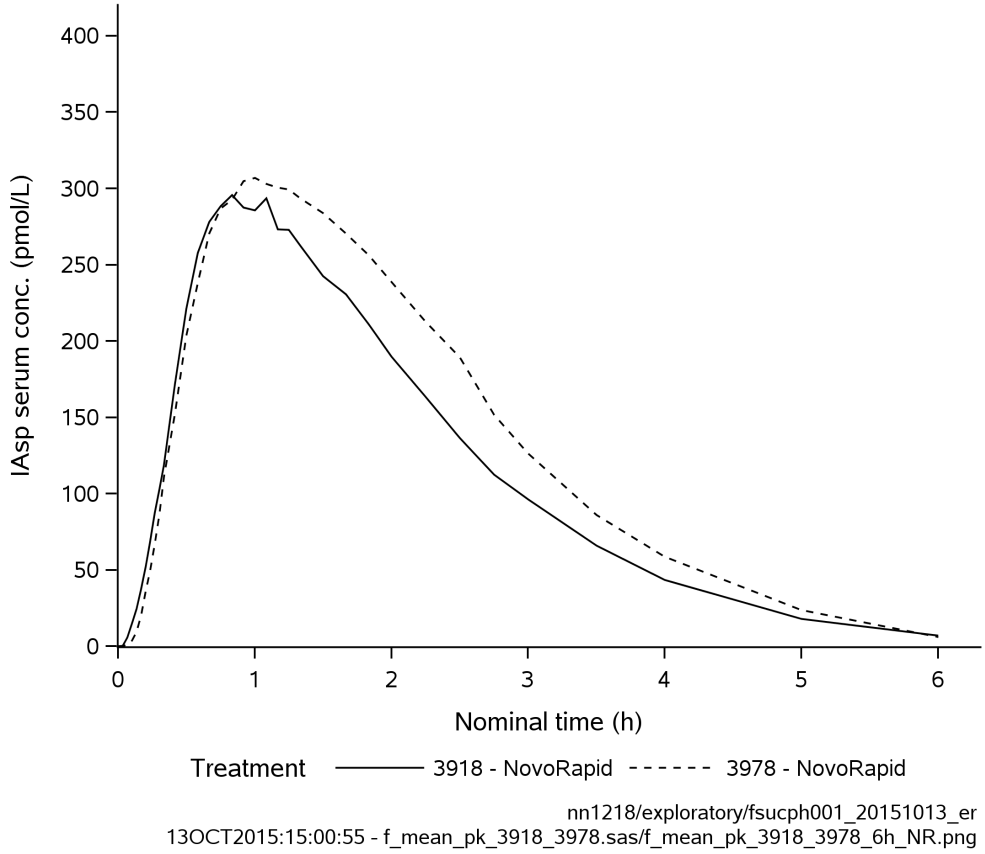
	N	Estimate	95% CI
AUCGIR(0-1h) (mg/kg)			
Within-subject CV (%)			
Faster Aspart	68	25.5	
NovoRapid	65	21.6	
Within-subject variance (log-scale)			
Faster Aspart		0.063	
NovoRapid		0.045	
Variance ratio			
Faster Aspart/NovoRapid		1.39	[0.75;2.56]

N: Number of profiles contributing to analysis, CI: Confidence interval
CV: Coefficient of variation
The endpoint was log-transformed and analysed using a linear mixed model with treatment as a fixed effect and subject as a random effect.
The between- and within-subject variances depend on treatment.

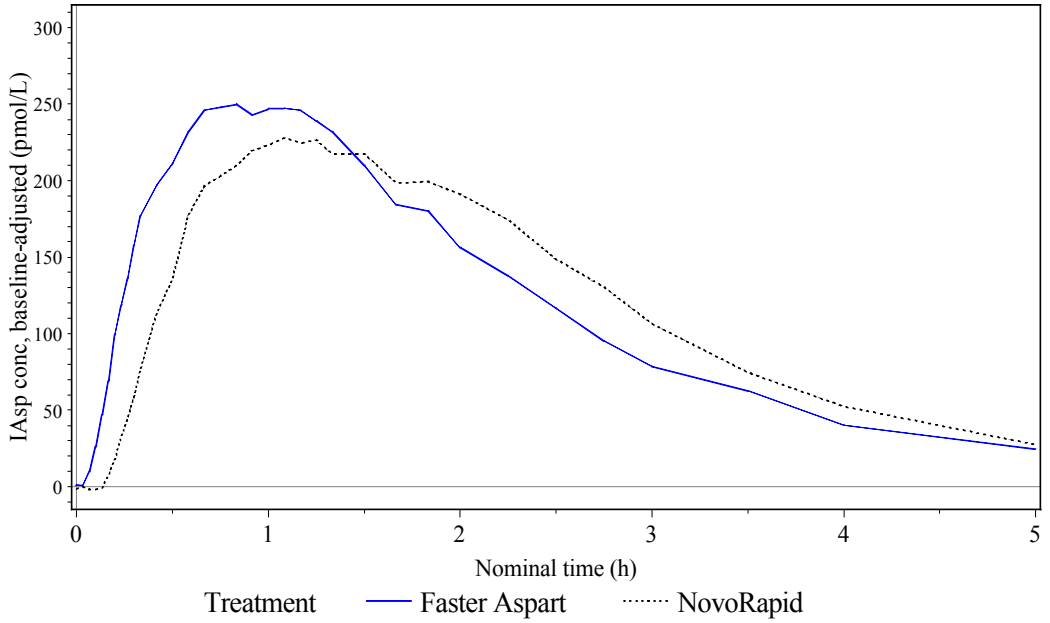
nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:37 - a_pkpd_variability.sas/a_pd_variability.txt



82: Insulin Aspart - mean profiles - trials 3918 and 3978



83: Insulin Aspart - mean profiles - trials 3918 and 3978



nn1218/exploratory/fsucph001_20151013_er
13OCT2015:15:01:01 - f_mean_pk_corr_3890.sas/f_mean_pk_corr_3890.cgm

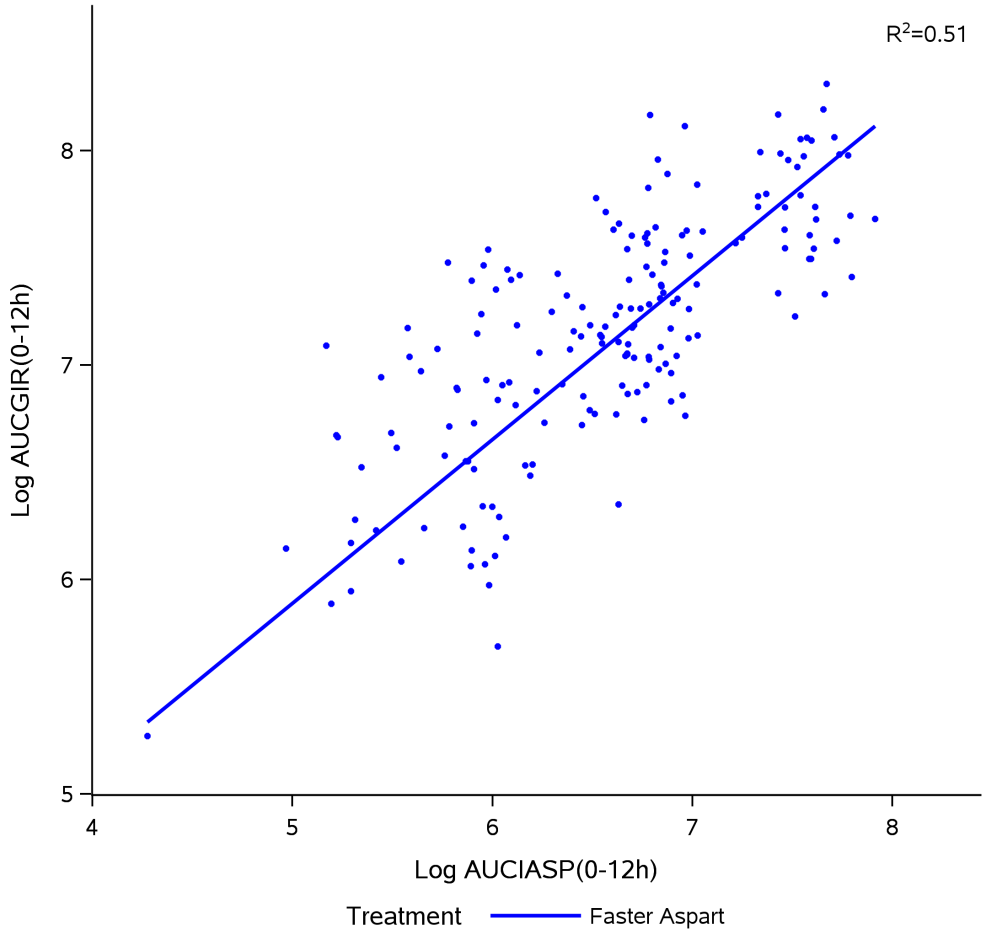
84: Mean (basal-insulin corrected) PK figure for trial 3890 - 0-5 hours

85: AUCGIR(0-12h) vs AUCIASP(0-12h) - estimated regression lines - trial 3887

Treatment	Parameter	Estimate	SE	N
Faster Aspart	Intercept	2.070	0.217	180
	Slope	0.764	0.026	

N: Number of profiles contributing to analysis, SE: Standard error.
The (log) PD endpoint was analysed in a linear model with treatment
and subject as fixed effects and the (log) PK parameter as covariate
with slope depending on treatment.

nn1218/exploratory/fsucph001_20151013_er
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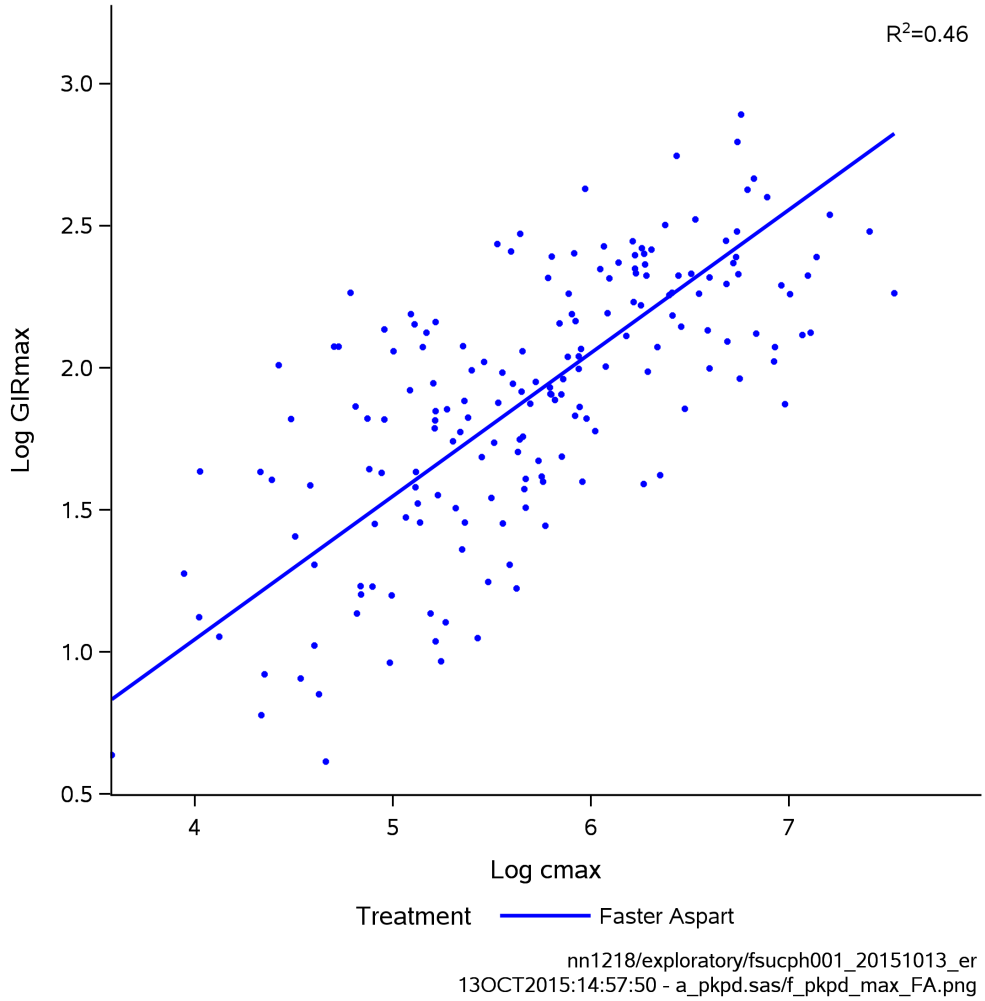
86: AUCGIR(0-12h) vs AUCIASP(0-12h) - estimated regression line - trial 3887 - faster aspart

87: GIRmax vs cmax - estimated regression lines - trial 3887

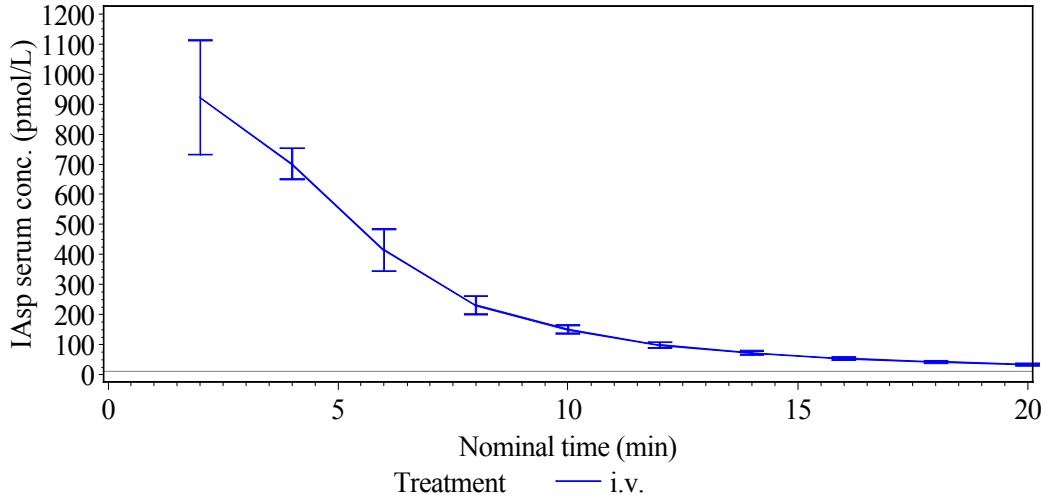
Treatment	Parameter	Estimate	SE	N
Faster Aspart	Intercept	-0.971	0.212	180
	Slope	0.504	0.028	

N: Number of profiles contributing to analysis, SE: Standard error.
The (log) PD endpoint was analysed in a linear model with treatment
and subject as fixed effects and the (log) PK parameter as covariate
with slope depending on treatment.

nn1218/exploratory/fsucph001_20151013_er
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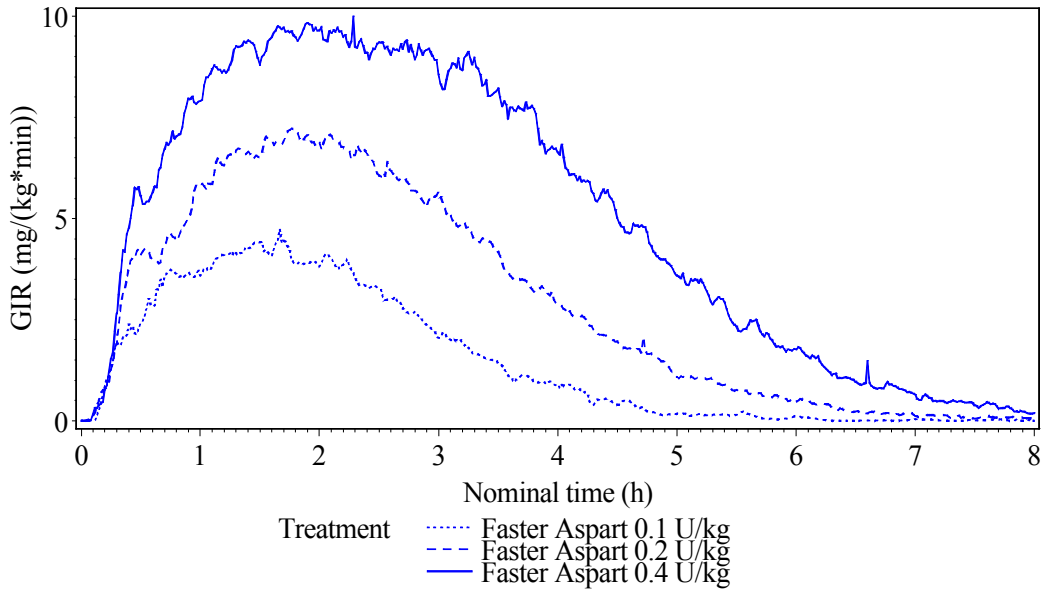
88: GIRmax vs cmax - estimated regression line - trial 3887 - faster aspart



Horizontal grey line at 10 pmol/L indicates the LLOQ

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:15:01:11 - f_mean_pk.sas/f_mean_pk_1_iv.cgm

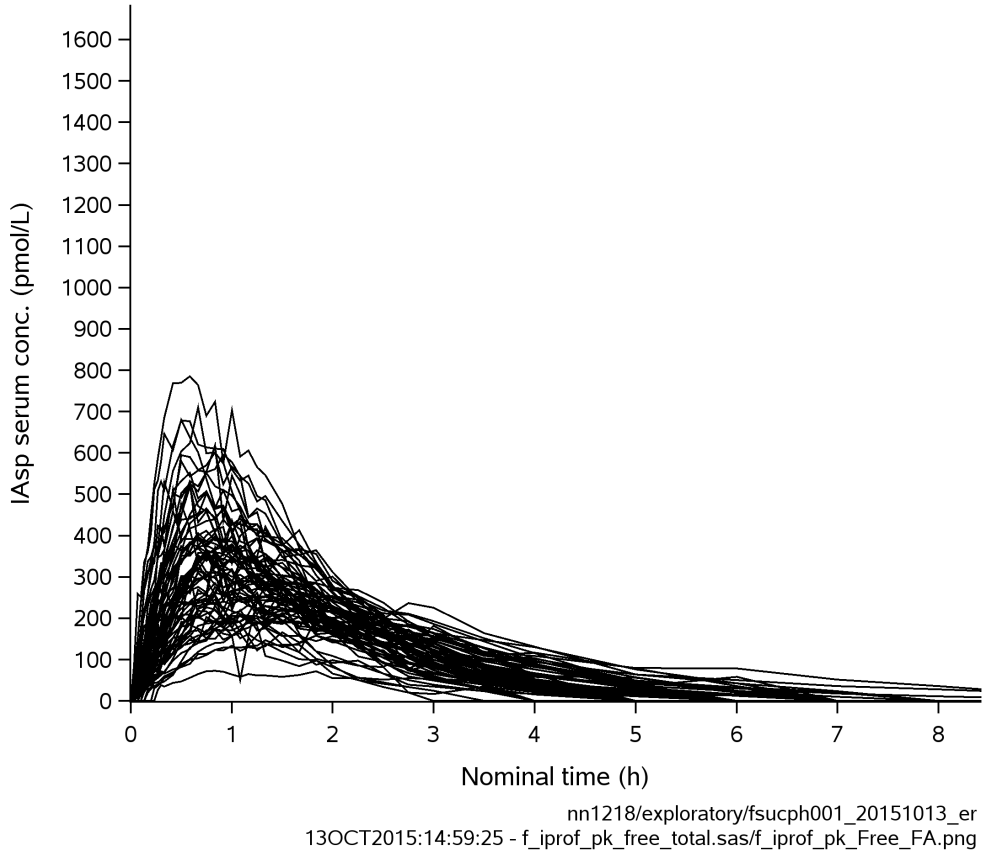
89: Insulin Aspart - mean profile - faster aspart - i.v. - trial 3949 FAS - full analysis set



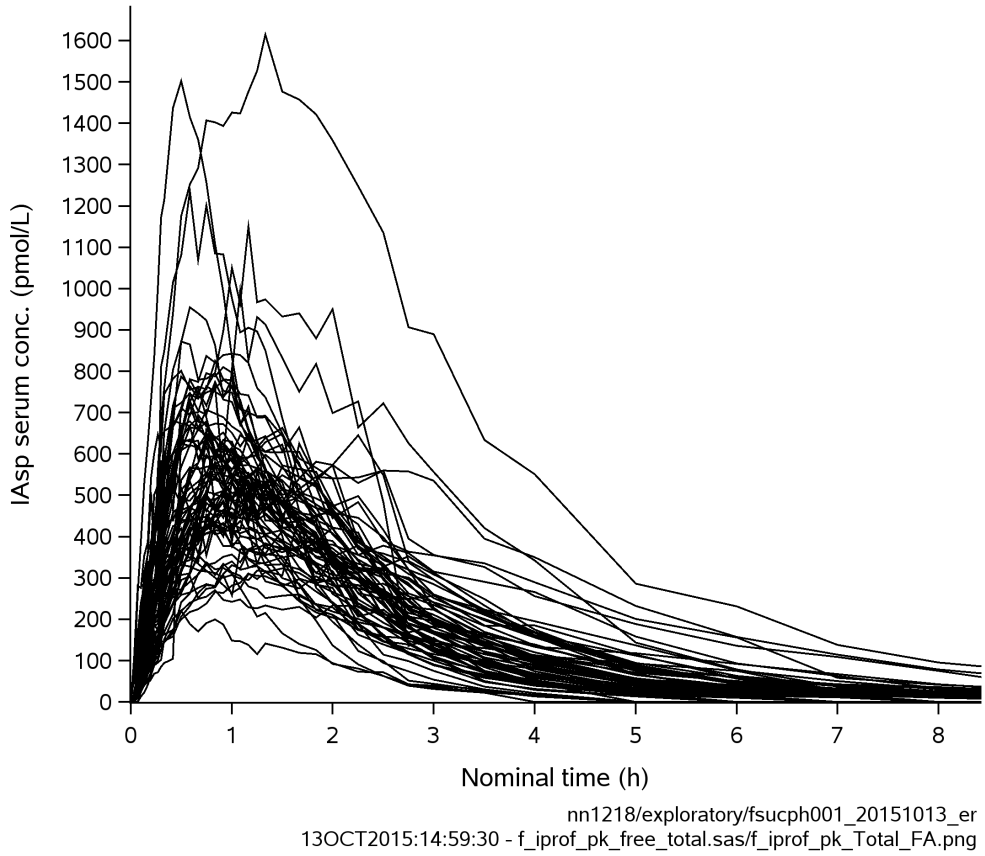
Repetitions of 0.2 U/kg have been replaced by their average

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:15:00:01 - f_mean_gir_strat.sas/f_mean_gir_strat_3887.cgm

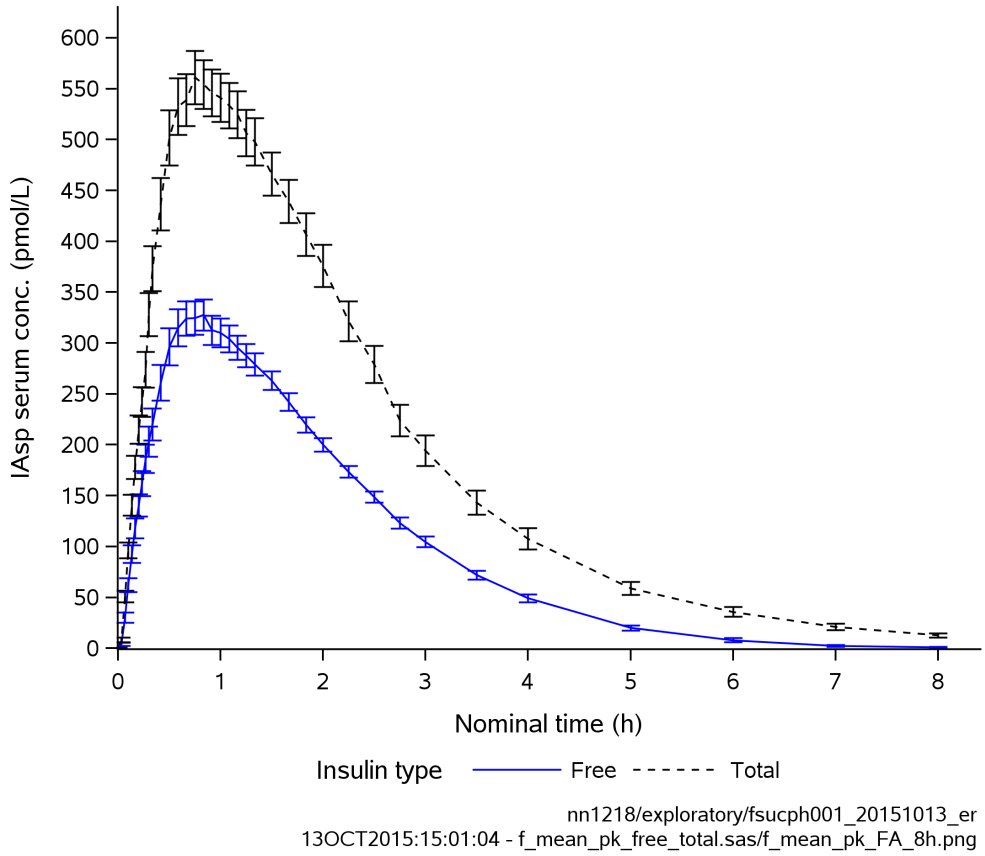
90: GIR - mean profiles by dose - faster aspart - trial 3887 - full analysis set



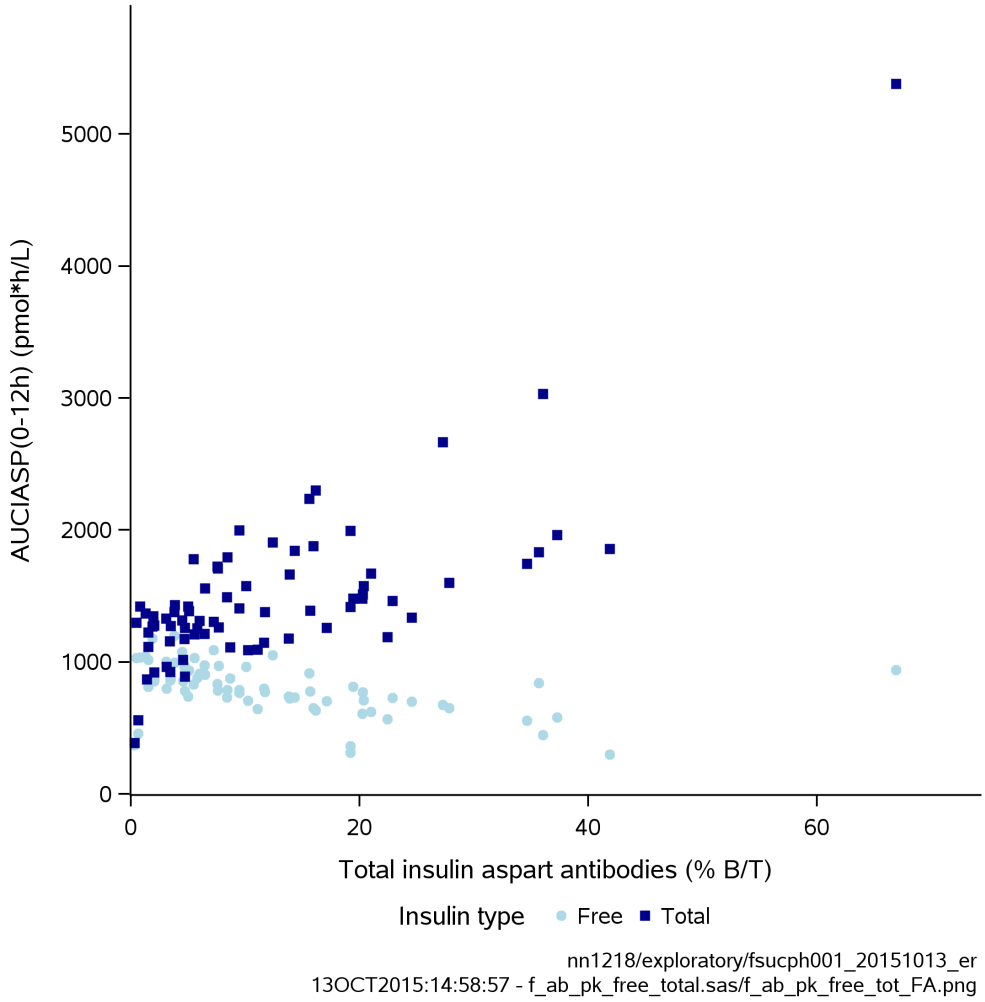
91: Free Insulin Aspart profiles - Faster Aspart - trials 3891,3978



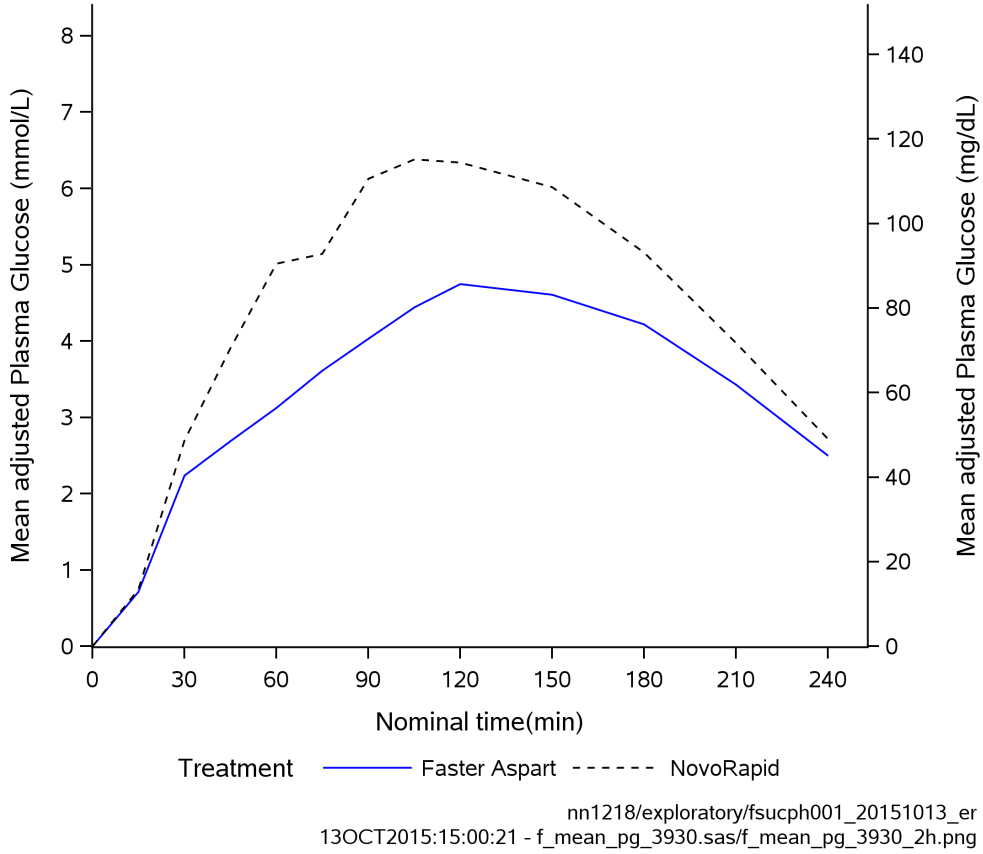
92: Total Insulin Aspart profiles - Faster Aspart - trials 3891,3978



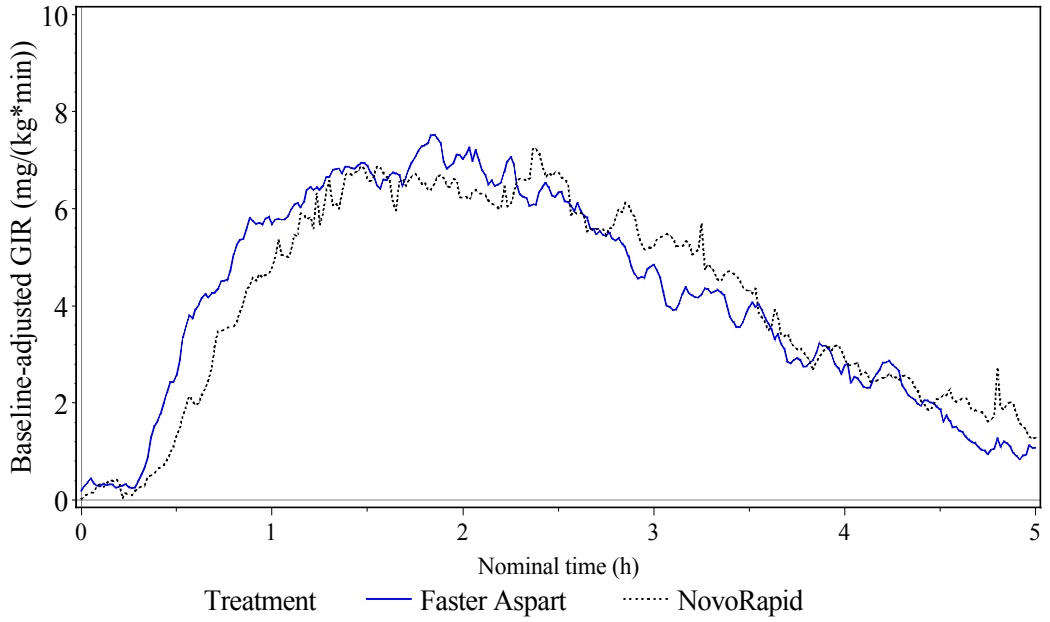
93: Insulin Aspart profiles - mean (sem) (0-8 hours) - Faster Aspart trials 3891,3978



94: Free and total IAsp AUC(0-12h) vs antibodies - trials 3891 and 3978, Faster Aspart

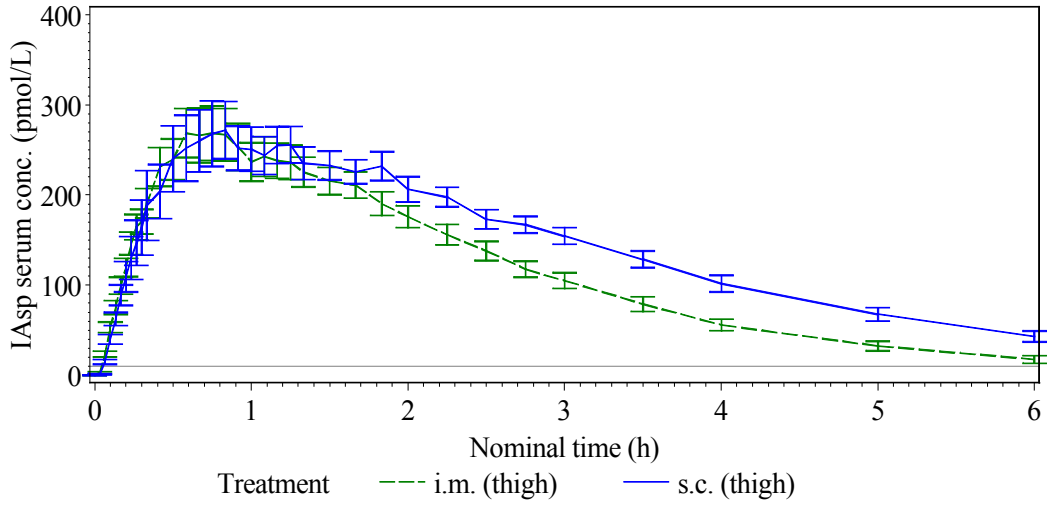


95: Meal test profiles - mean baseline adjusted PG profiles - trial 3930



nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:59:55 - f_mean_gir_corr_3890.sas/f_mean_gir_corr_3890.cgm

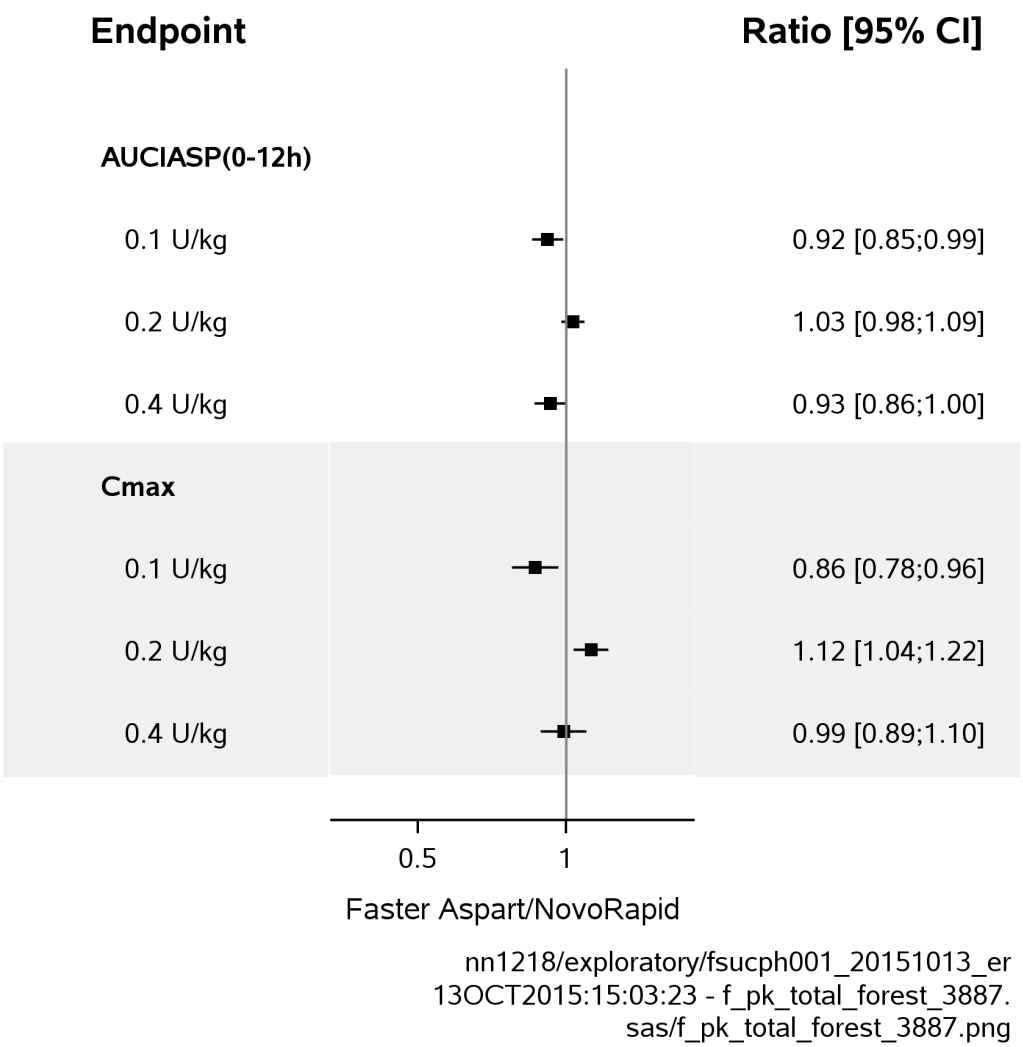
96: Mean (basal-insulin corrected) GIR figure for trial 3890 - 0-5 hours



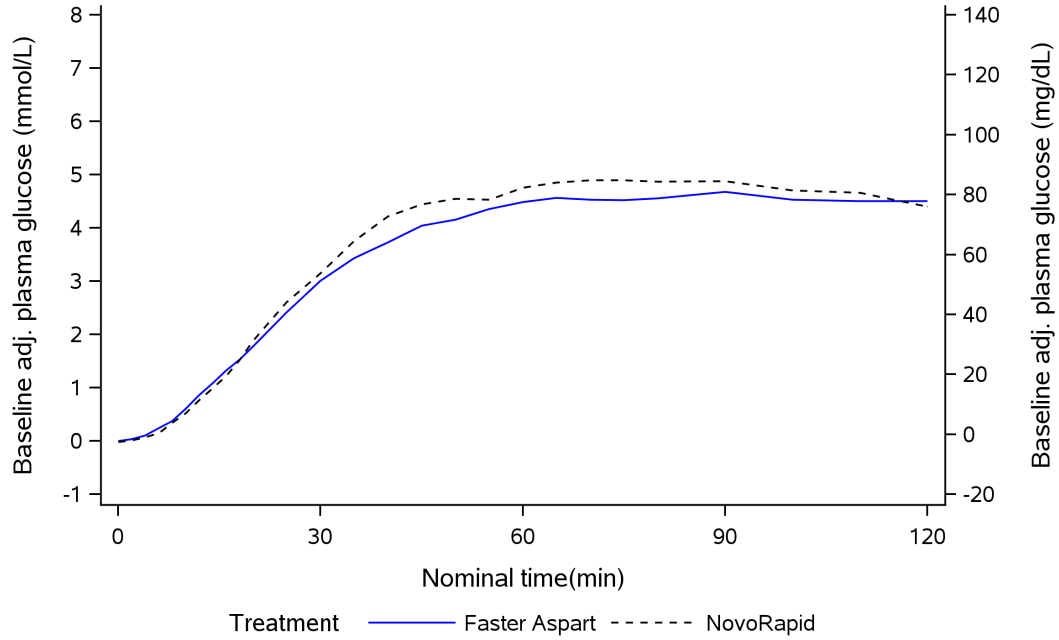
Horizontal grey line at 10 pmol/L indicates the LLOQ

nn1218/exploratory/fsucph001_20151013_er
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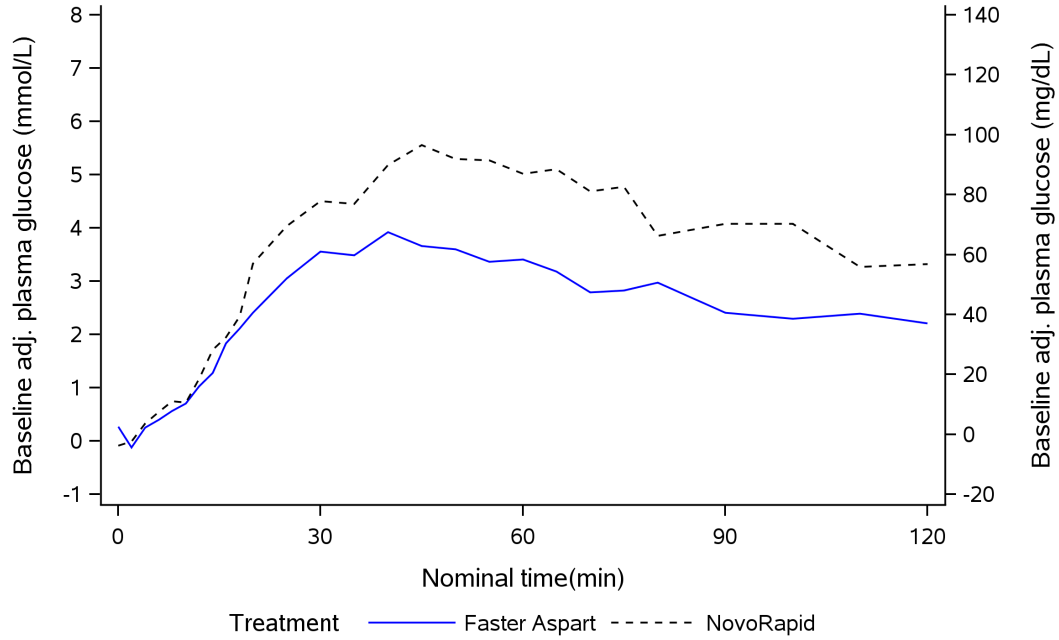
97: Insulin Aspart - mean (SEM) profiles - Faster Aspart - i.m. (thigh) + s.c. (thigh) - trial 3949 - full analysis set



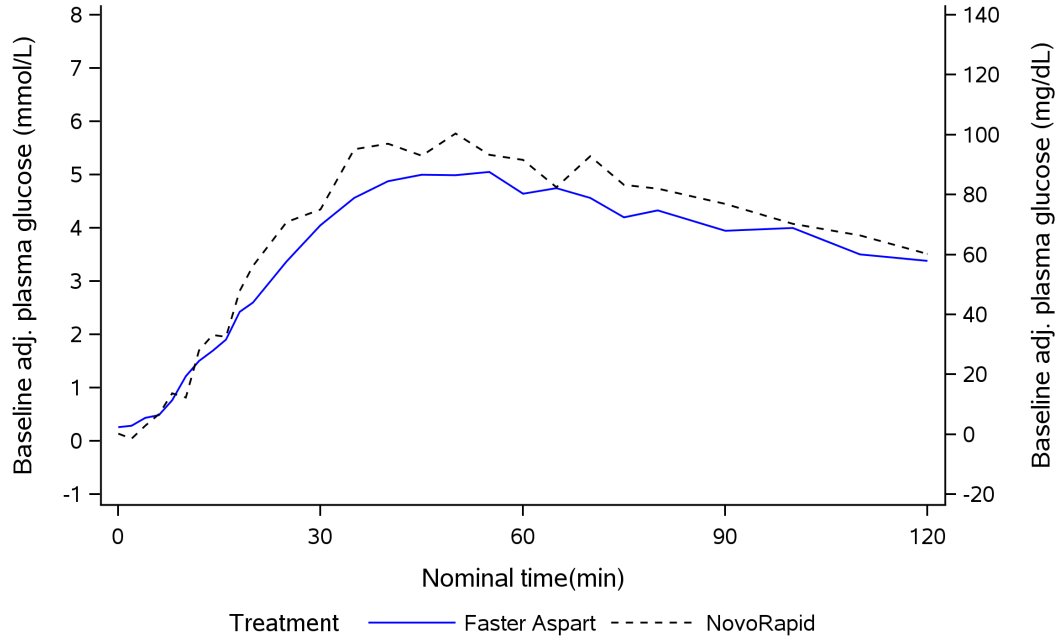
98: Insulin Aspart endpoints - AUCIASP(0-12h) and Cmax - forest plot of treatment ratio by dose - trial 3887



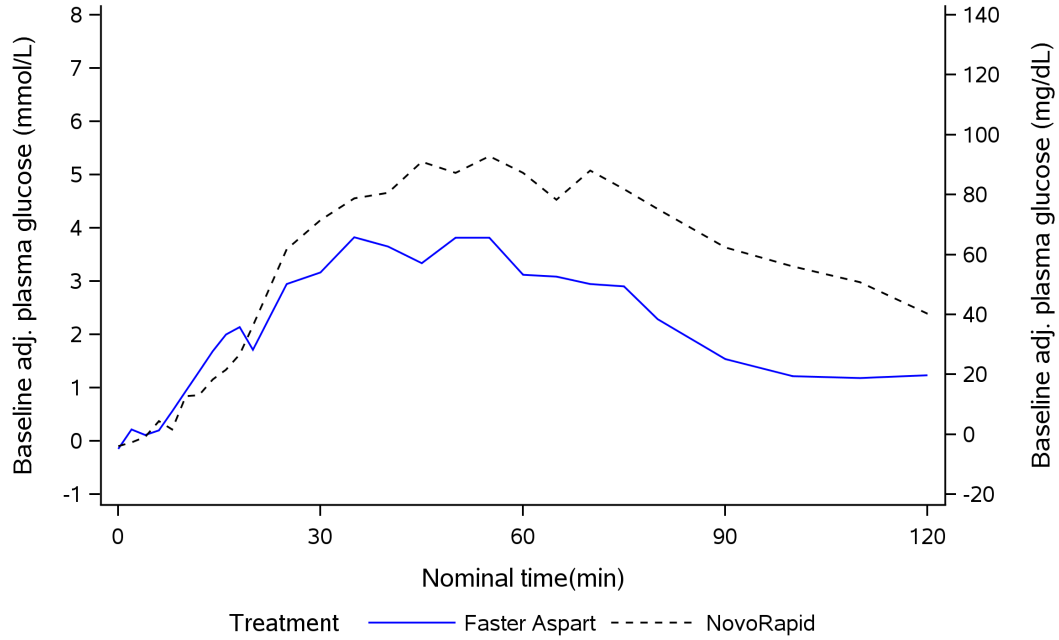
99: Mean baseline adjusted PG (0-2 hours) - trial 3889 FAS



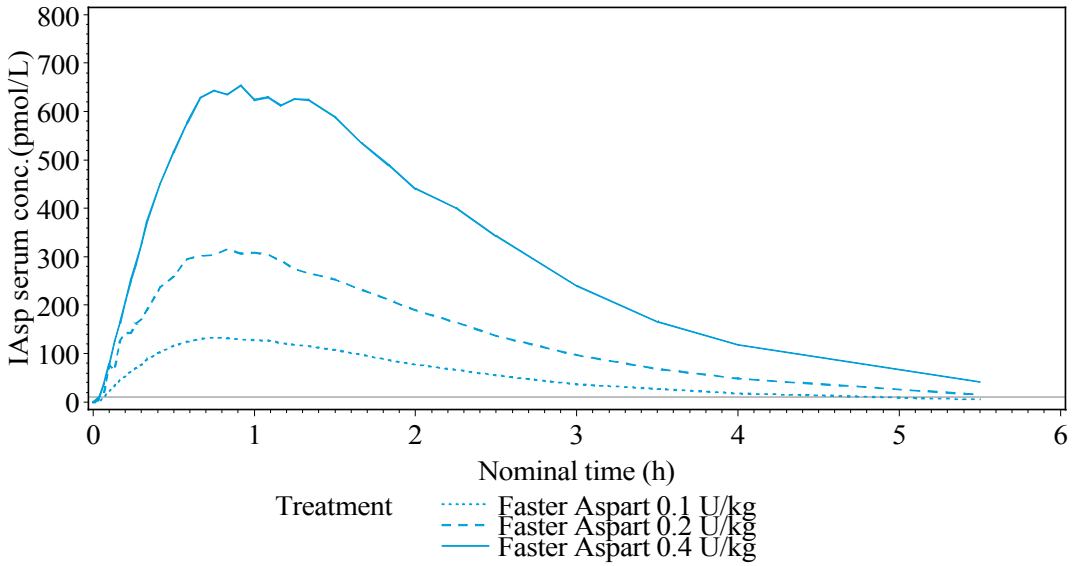
100: Mean baseline adjusted PG (0-2 hours) - trial 3888 - children - FAS



101: Mean baseline adjusted PG (0-2 hours) - trial 3888 - adolescents - FAS



102: Mean baseline adjusted PG (0-2 hours) - trial 3888 - adults - FAS



Repetitions of 0.2 U/kg have been replaced by their average
Horizontal grey line at 10 pmol/L indicates the LLOQ

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:15:01:12 - f_mean_pk_strat_3887.sas/f_mean_pk_1FA.cgm

103: Insulin Aspart - mean profiles - Faster Aspart - trial 3887 full analysis set - full analysis set

104: Insulin aspart endpoints - descriptive statistics - trial 3978 - full analysis set

	FIA (Q)	NovoRapid
AUC(0-90min) (pmol*h/L)		
N	51	51
Mean (StD)	358.05 (141.58)	323.07 (133.98)
Median	346.93	288.91
Geometric mean (CV)	328.62 (39.54)	294.94 (41.47)
Min;Max	75.85; 785.09	78.64; 703.43
Time to 50% Cmax (min)		
N	51	51
Mean (StD)	20.67 (7.41)	31.55 (7.06)
Median	20.00	30.00
Geometric mean (CV)	19.36 (35.85)	30.74 (22.38)
Min;Max	8.00; 35.00	16.00; 45.00
Onset of appearance (min)		
N	51	51
Mean (StD)	3.58 (1.89)	8.87 (3.35)
Median	3.18	8.15
Geometric mean (CV)	3.15 (52.77)	8.26 (37.75)
Min;Max	0.66; 9.22	2.97; 19.28

StD: standard deviation, CV: Coefficient of variation.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:15:04:11 - t_sum_pkpd_3878.sas/t_sum_pk_3978.txt

105: GIR endpoints - descriptive statistics - trial 3978 - full analysis set

	FIA (Q)	NovoRapid
Time to 50% GIRmax (min)		
N	51	51
Mean (StD)	38.31 (20.03)	46.06 (16.28)
Median	34.00	45.00
Min;Max	0.00; 129.00	0.00; 83.00

StD: standard deviation, CV: Coefficient of variation.

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:15:04:11 - t_sum_pkpd_3878.sas/t_sum_pd_3978.txt

106: GIR AUCs and GIRmax - treatment and BMI ratios - adults, trials 3887,3891,3978

	N	Estimate	95% CI	P-value
AUCGIR(0-1h)(mg/kg)				
Faster Aspart	253			
NovoRapid	247			
Faster Aspart/NovoRapid - BMI 20		1.31	[1.15;1.50]	<0.001
Faster Aspart/NovoRapid - BMI 24		1.33	[1.24;1.42]	<0.001
Faster Aspart/NovoRapid - BMI 28		1.34	[1.21;1.48]	<0.001
BMI 20/BMI 24 - Faster Aspart		1.47	[1.30;1.67]	<0.001
BMI 20/BMI 24 - NovoRapid		1.49	[1.31;1.69]	<0.001
BMI 20/BMI 28 - Faster Aspart		2.04	[1.61;2.58]	<0.001
BMI 20/BMI 28 - NovoRapid		2.09	[1.65;2.64]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.39	[1.25;1.54]	<0.001
BMI 24/BMI 28 - NovoRapid		1.40	[1.26;1.56]	<0.001
Treatment*BMI Interaction				0.832
AUCGIR(0-90min)(mg/kg)				
Faster Aspart	253			
NovoRapid	248			
Faster Aspart/NovoRapid - BMI 20		1.23	[1.09;1.38]	<0.001
Faster Aspart/NovoRapid - BMI 24		1.19	[1.12;1.26]	<0.001
Faster Aspart/NovoRapid - BMI 28		1.16	[1.06;1.27]	0.001
BMI 20/BMI 24 - Faster Aspart		1.47	[1.29;1.66]	<0.001
BMI 20/BMI 24 - NovoRapid		1.42	[1.25;1.61]	<0.001
BMI 20/BMI 28 - Faster Aspart		2.03	[1.61;2.56]	<0.001
BMI 20/BMI 28 - NovoRapid		1.92	[1.52;2.42]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.38	[1.24;1.54]	<0.001
BMI 24/BMI 28 - NovoRapid		1.35	[1.21;1.50]	<0.001
Treatment*BMI Interaction				0.519
AUCGIR(0-2h)(mg/kg)				
Faster Aspart	253			
NovoRapid	248			
Faster Aspart/NovoRapid - BMI 20		1.16	[1.04;1.30]	0.009
Faster Aspart/NovoRapid - BMI 24		1.13	[1.06;1.19]	<0.001
Faster Aspart/NovoRapid - BMI 28		1.10	[1.00;1.20]	0.043
BMI 20/BMI 24 - Faster Aspart		1.42	[1.26;1.60]	<0.001
BMI 20/BMI 24 - NovoRapid		1.37	[1.22;1.55]	<0.001
BMI 20/BMI 28 - Faster Aspart		1.91	[1.53;2.39]	<0.001
BMI 20/BMI 28 - NovoRapid		1.80	[1.44;2.25]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.35	[1.21;1.49]	<0.001
BMI 24/BMI 28 - NovoRapid		1.31	[1.18;1.45]	<0.001
Treatment*BMI Interaction				0.467
AUCGIR(0-12h)(mg/kg)				
Faster Aspart	253			
NovoRapid	248			
Faster Aspart/NovoRapid - BMI 20		1.07	[0.97;1.18]	0.202
Faster Aspart/NovoRapid - BMI 24		0.99	[0.94;1.04]	0.708
Faster Aspart/NovoRapid - BMI 28		0.93	[0.86;1.00]	0.066
BMI 20/BMI 24 - Faster Aspart		1.14	[1.04;1.25]	0.007
BMI 20/BMI 24 - NovoRapid		1.05	[0.96;1.16]	0.254
BMI 20/BMI 28 - Faster Aspart		1.27	[1.07;1.50]	0.007
BMI 20/BMI 28 - NovoRapid		1.10	[0.93;1.31]	0.254
BMI 24/BMI 28 - Faster Aspart		1.11	[1.03;1.21]	0.007
BMI 24/BMI 28 - NovoRapid		1.05	[0.97;1.13]	0.254

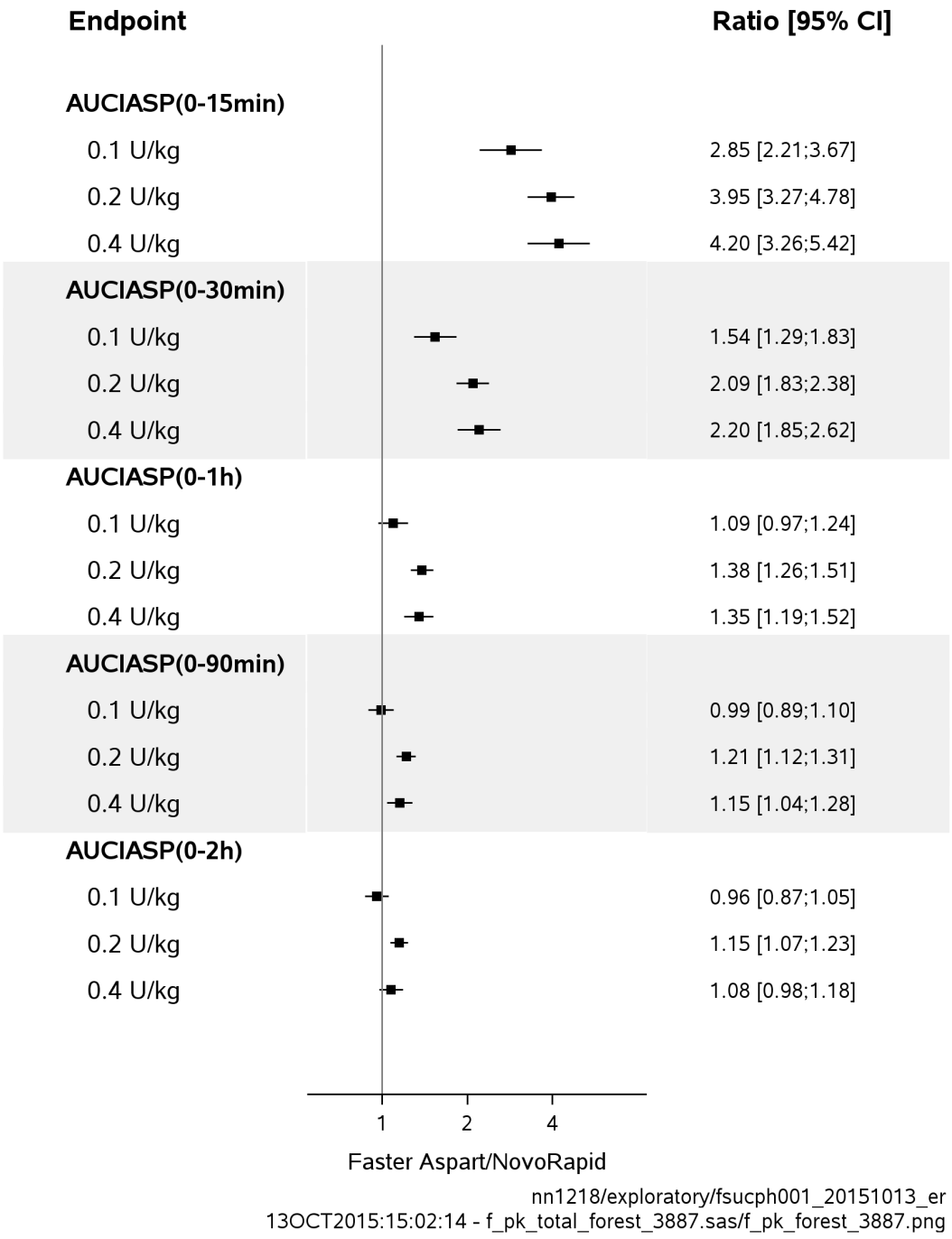
Treatment*BMI Interaction	0.064

GIR AUCs and GIRmax - treatment and BMI ratios -
adults, trials 3887,3891,3978

	N	Estimate	95% CI	P-value
GIRmax (mg/(kg*min))				
Faster Aspart	253			
NovoRapid	248			
Faster Aspart/NovoRapid - BMI 20		1.08	[0.97;1.19]	0.150
Faster Aspart/NovoRapid - BMI 24		1.01	[0.96;1.06]	0.752
Faster Aspart/NovoRapid - BMI 28		0.95	[0.88;1.03]	0.235
BMI 20/BMI 24 - Faster Aspart		1.32	[1.19;1.46]	<0.001
BMI 20/BMI 24 - NovoRapid		1.23	[1.12;1.36]	<0.001
BMI 20/BMI 28 - Faster Aspart		1.67	[1.39;2.00]	<0.001
BMI 20/BMI 28 - NovoRapid		1.48	[1.23;1.77]	<0.001
BMI 24/BMI 28 - Faster Aspart		1.26	[1.16;1.37]	<0.001
BMI 24/BMI 28 - NovoRapid		1.19	[1.10;1.30]	<0.001
Treatment*BMI Interaction				0.105

N: Number of profiles contributing to analysis, CI: Confidence Interval.
The endpoint was log-transformed and analysed in a linear mixed model with
period(trial), treatment*dose-factor, treatment*log(BMI) as fixed effects
and subject as a random effect.
One value of AUC(0-1h) was 0 and therefore excluded (NovoRapid 0.1 U/kg)

nn1218/exploratory/fsucph001_20151013_er
13OCT2015:14:58:19 - a_pkpd_bmi.sas/a_gir_bmi.txt



107: Insulin Aspart endpoints - AUCIASP - forest plot of treatment ratio by dose - trial 3887

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.2.5. 付録

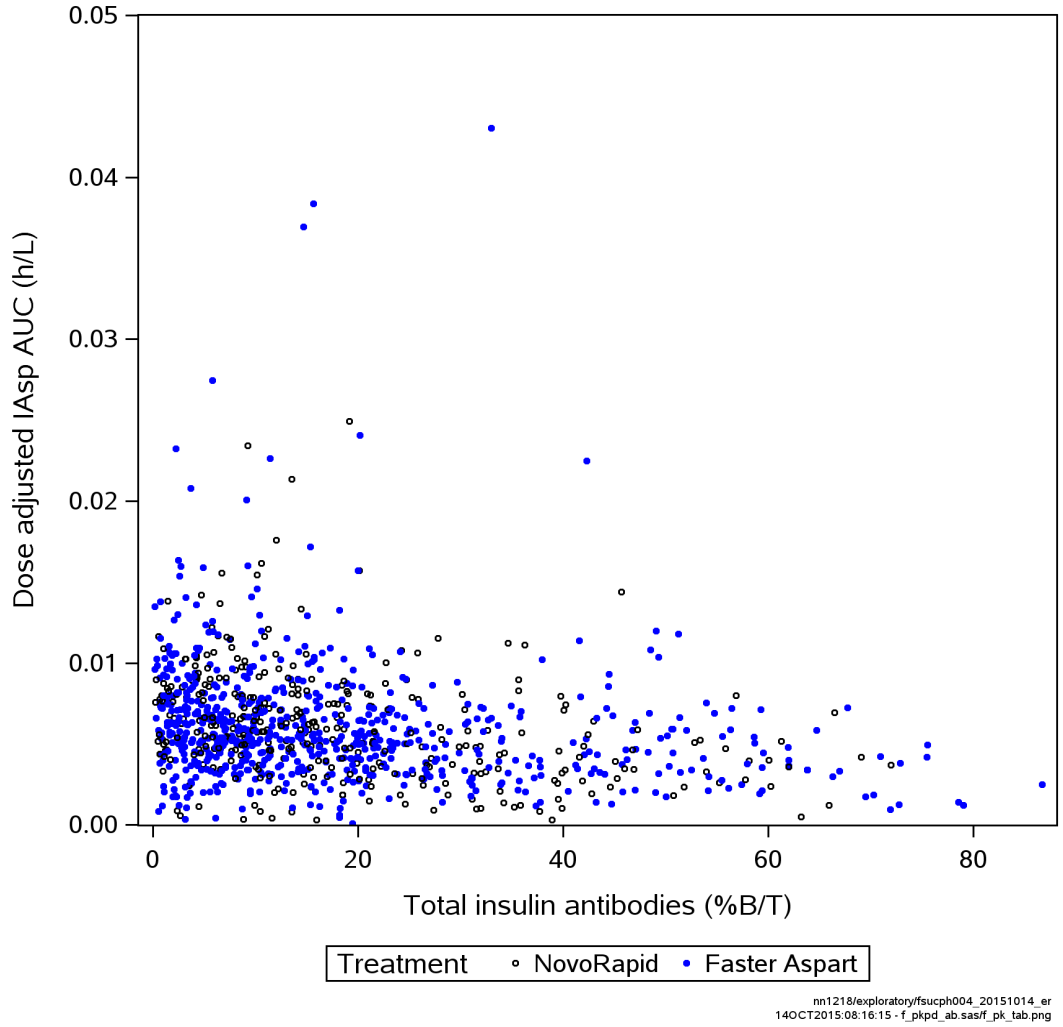
4. 3852 試験の結果に基づく図表

ノボ ノルディスク ファーマ株式会社

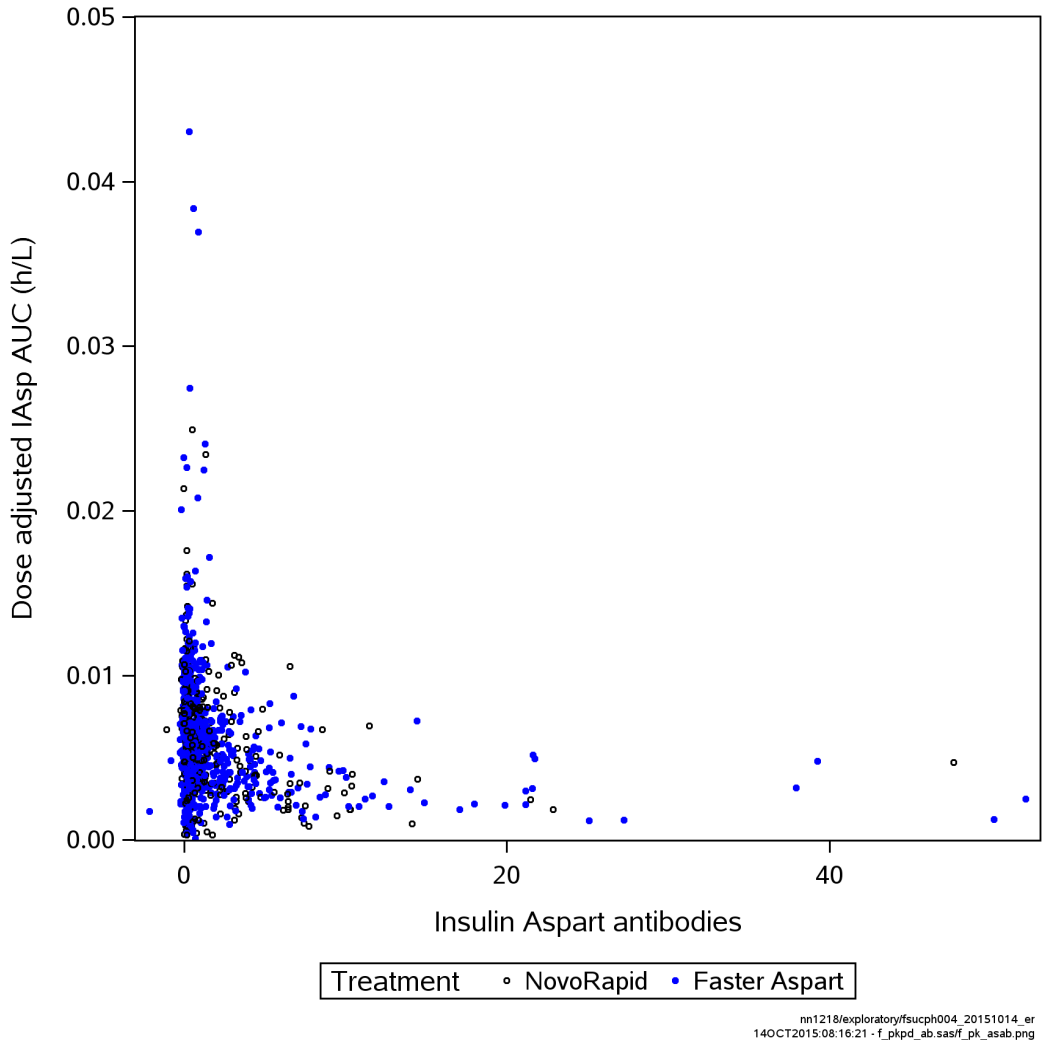
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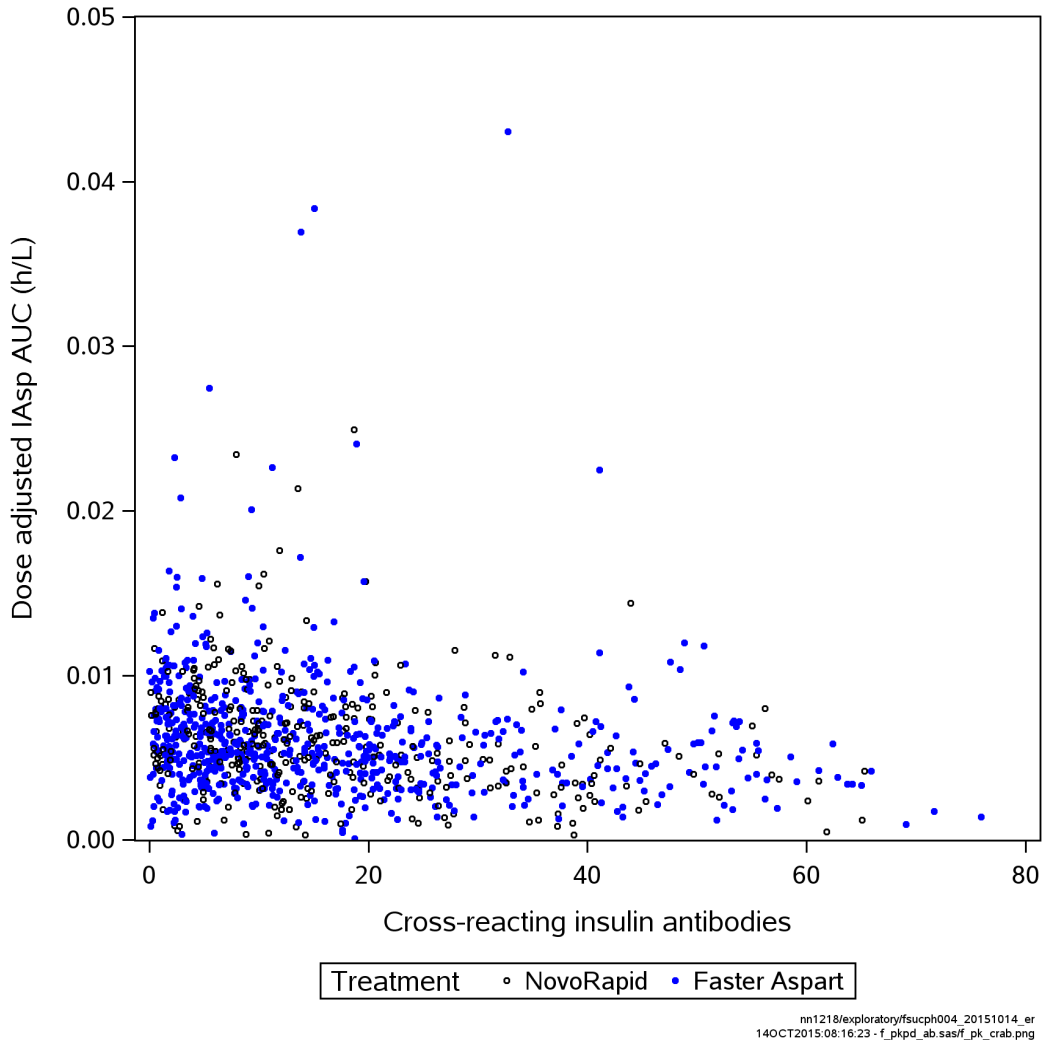
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2: Dose adjusted predicted IAsp AUC vs. IAsp antibodies - trial 3852 in T1DM patients - FAS



3: Dose adjusted predicted IAsp AUC vs. CR antibodies - trial 3852 in T1DM patients - FAS

4: Statistical analysis of model predicted IAsp AUC after meal-test (week 26) including total antibody as covariate - phase 3 trial 3852 in T1DM patients - full analysis set

	Estimate	95% CI	N	P-value
LSmeans				
Faster Aspart - Female	286.35		289	
Faster Aspart - Male	221.64		393	
NovoRapid - Female	283.56		131	
NovoRapid - Male	226.06		217	
Faster Aspart - EUROPE	246.16		289	
Faster Aspart - NORTH AMERICA	247.71		393	
NovoRapid - EUROPE	254.08		145	
NovoRapid - NORTH AMERICA	240.71		203	
Faster Aspart - AMERICAN INDIAN OR ALASK	189.81		1	
Faster Aspart - ASIAN	307.93		4	
Faster Aspart - BLACK	187.84		13	
Faster Aspart - NA	261.77		16	
Faster Aspart - NATIVE HAWAIIAN OR OTHER	304.42		1	
Faster Aspart - OTHER	253.60		3	
Faster Aspart - WHITE	247.72		644	
NovoRapid - ASIAN	273.43		6	
NovoRapid - BLACK	256.08		8	
NovoRapid - NA	298.91		11	
NovoRapid - NATIVE HAWAIIAN OR OTHER PAC	214.35		2	
NovoRapid - OTHER	250.49		3	
NovoRapid - WHITE	243.99		318	
Faster Aspart - HISPANIC	261.30		52	
Faster Aspart - NOT HISPANIC	245.91		630	
NovoRapid - HISPANIC	351.91		16	
NovoRapid - NOT HISPANIC	241.99		332	
Faster Aspart - mild renal failure	282.51		115	
Faster Aspart - moderate renal failure	330.22		21	
Faster Aspart - normal renal function	237.51		546	
NovoRapid - mild renal failure	324.37		45	
NovoRapid - moderate renal failure	281.32		8	
NovoRapid - normal renal function	235.20		295	
Ratios and slopes				
females - FA/NR	1.01	[0.88;1.16]		0.890
males - FA/NR	0.98	[0.88;1.09]		0.723
FA - females/males	1.29	[1.16;1.44]		<0.001
NR - females/males	1.25	[1.07;1.47]		0.006
FA - Europe/North America	0.99	[0.90;1.09]		0.899
NR - Europe/North America	1.06	[0.92;1.21]		0.433
Europe - FA/NR	0.97	[0.86;1.10]		0.616
North America - FA/NR	1.03	[0.93;1.14]		0.591
FA - Asian/White	1.24	[0.69;2.25]		0.471
FA - Black/White	0.76	[0.54;1.06]		0.104
NR - Asian/White	1.12	[0.68;1.84]		0.651
NR - Black/White	1.05	[0.68;1.62]		0.827
Asian - FA/NR	1.13	[0.52;2.42]		0.761
Black - FA/NR	0.73	[0.43;1.26]		0.261
White - FA/NR	1.02	[0.94;1.10]		0.714
FA - Hispanic/not Hispanic	1.06	[0.89;1.27]		0.500
NR - Hispanic/not Hispanic	1.45	[1.07;1.98]		0.017
Hispanic - FA/NR	0.74	[0.53;1.05]		0.089
not Hispanic - FA/NR	1.02	[0.94;1.10]		0.694

normal renal - FA/NR	1.01	[0.92;1.10]	0.830
mild renal failure - FA/NR	0.87	[0.69;1.10]	0.250
moderate renal failure - FA/NR	1.17	[0.70;1.96]	0.540
FA - mild renal failure/normal	1.19	[1.03;1.37]	0.017
FA - moderate renal failure/normal	1.39	[1.05;1.85]	0.023
NR - mild renal failure/normal	1.38	[1.10;1.72]	0.005

Statistical analysis of model predicted IAsp AUC after meal-test (week 26) including total antibody as covariate - phase 3 trial 3852 in T1DM patients - full analysis set

	Estimate	95% CI	N	P-value
NR - moderate renal failure/normal	1.20	[0.77;1.87]		0.431
FA - weight slope	1.00	[0.71;1.29]		<0.001
NR - weight slope	0.77	[0.31;1.22]		<0.001
FA - age slope	-0.02	[-0.18;0.13]		0.751
NR - age slope	-0.08	[-0.29;0.14]		0.482
ab 25th percentile - FA/NR	0.98	[0.82;1.17]		0.801
ab 50th percentile - FA/NR	1.05	[0.89;1.23]		0.593
ab 75th percentile - FA/NR	1.13	[0.95;1.35]		0.158
FA - ab 50th/25th percentiles	0.93	[0.90;0.95]		<0.001
FA - ab 75th/25th percentiles	0.85	[0.80;0.91]		<0.001
NR - ab 50th/25th percentiles	0.86	[0.82;0.90]		<0.001
NR - ab 75th/25th percentiles	0.73	[0.66;0.81]		<0.001

N: Number of subjects, CI: confidence interval.
The log-transformed endpoint was analysed using a linear model with treatment-dependent fixed effects of sex, geographic region, race, ethnicity, renal function, log(1+(ab/median ab)), log(bodyweight), and log(age) - where ab is antibody level.
The Faster aspart group consists of subjects in Faster aspart (meal) arm or Faster aspart (post) arm.

nn1218/exploratory/fsucph004_20151014_er
14OCT2015:08:13:43 - a_pk_cov.sas/a_pk_cov.txt

5: Statistical analysis of model predicted IAsp AUC after meal-test (week 26) including aspart antibody as covariate - phase 3 trial 3852 in T1DM patients - full analysis set

	Estimate	95% CI	P-value
Ratios			
ab 25th percentile - FA/NR	1.07	[0.91;1.26]	0.418
ab 50th percentile - FA/NR	1.09	[0.93;1.28]	0.277
ab 75th percentile - FA/NR	1.13	[0.96;1.34]	0.147
FA - ab 50th/25th percentiles	0.93	[0.91;0.95]	<0.001
FA - ab 75th/25th percentiles	0.82	[0.77;0.86]	<0.001
NR - ab 50th/25th percentiles	0.91	[0.88;0.94]	<0.001
NR - ab 75th/25th percentiles	0.77	[0.71;0.84]	<0.001

CI: confidence interval.
The log-transformed endpoint was analysed using a linear model with treatment-dependent fixed effects of sex, geographic region, race, ethnicity, renal function, log(1+(ab/median ab)), log(bodyweight), and log(age) - where ab is antibody level.
The Faster aspart group consists of subjects in Faster aspart (meal) arm or Faster aspart (post) arm.

nn1218/exploratory/fsucph004_20151014_er
14OCT2015:08:14:03 - a_pk_cov_aspart_ab.sas/a_pk_cov_asp.txt

6: Statistical analysis of model predicted IAsp AUC after meal-test (week 26) including cross reacting antibody as covariate - phase 3 trial 3852 in T1DM patients - full analysis set

	Estimate	95% CI	P-value
Ratios			
ab 25th percentile - FA/NR	0.97	[0.81;1.16]	0.765
ab 50th percentile - FA/NR	1.04	[0.88;1.23]	0.663
ab 75th percentile - FA/NR	1.12	[0.94;1.34]	0.196
FA - ab 50th/25th percentiles	0.95	[0.92;0.97]	<0.001
FA - ab 75th/25th percentiles	0.88	[0.82;0.94]	<0.001
NR - ab 50th/25th percentiles	0.89	[0.85;0.93]	<0.001
NR - ab 75th/25th percentiles	0.76	[0.69;0.85]	<0.001

CI: confidence interval.
The log-transformed endpoint was analysed using a linear model with treatment-dependent fixed effects of sex, geographic region, race, ethnicity, renal function, log(1+(ab/median ab)), log(bodyweight), and log(age) - where ab is antibody level.
The Faster aspart group consists of subjects in Faster aspart (meal) arm or Faster aspart (post) arm.

nn1218/exploratory/fsucph004_20151014_er
14OCT2015:08:14:42 - a_pk_cov_cr_ab.sas/a_pk_cov_cr.txt

7: Statistical analysis of model predicted dose adjusted IAsp AUC vs BMI - after meal-test (week 26) - phase 3 trial 3852 in T1DM patients - full analysis set

	Estimate	95% CI	P-value
Slopes			
FA - BMI slope	0.03	[-0.30;0.35]	0.875
NR - BMI slope	0.03	[-0.47;0.54]	0.899
Faste Aspart vs. NovoRapid - BMI slope	-0.01	[-0.61;0.59]	0.982

CI: confidence interval.
The log-transformed endpoint was analysed using a linear model with treatment-dependent fixed effects of sex, geographic region, race, ethnicity, renal function, log(1+(ab/median ab)), log(bmi), and log(age) - where ab is antibody level.
The Faster aspart group consists of subjects in Faster aspart (meal) arm or Faster aspart (post) arm.

nn1218/exploratory/fsucph004_20151014_er
14OCT2015:08:14:23 - a_pk_cov_bmi.sas/a_pk_cov_bmi.txt

8: Statistical analysis of model predicted IAsp AUC vs age - no renal adjustment - after meal-test (week 26) including total antibody as covariate - phase 3 trial 3852 in T1DM patients - full analysis set

	Estimate	95% CI	P-value
Slopes			
FA - age slope	0.08	[-0.06;0.22]	0.241
NR - age slope	0.05	[-0.14;0.25]	0.581

CI: confidence interval.
The log-transformed endpoint was analysed using a linear model with treatment-dependent fixed effects of sex, geographic region, race, ethnicity, log(1+(ab/median ab)), log(bodyweight), and log(age) - where ab is antibody level.
The Faster aspart group consists of subjects in Faster aspart (meal) arm or Faster aspart (post) arm.

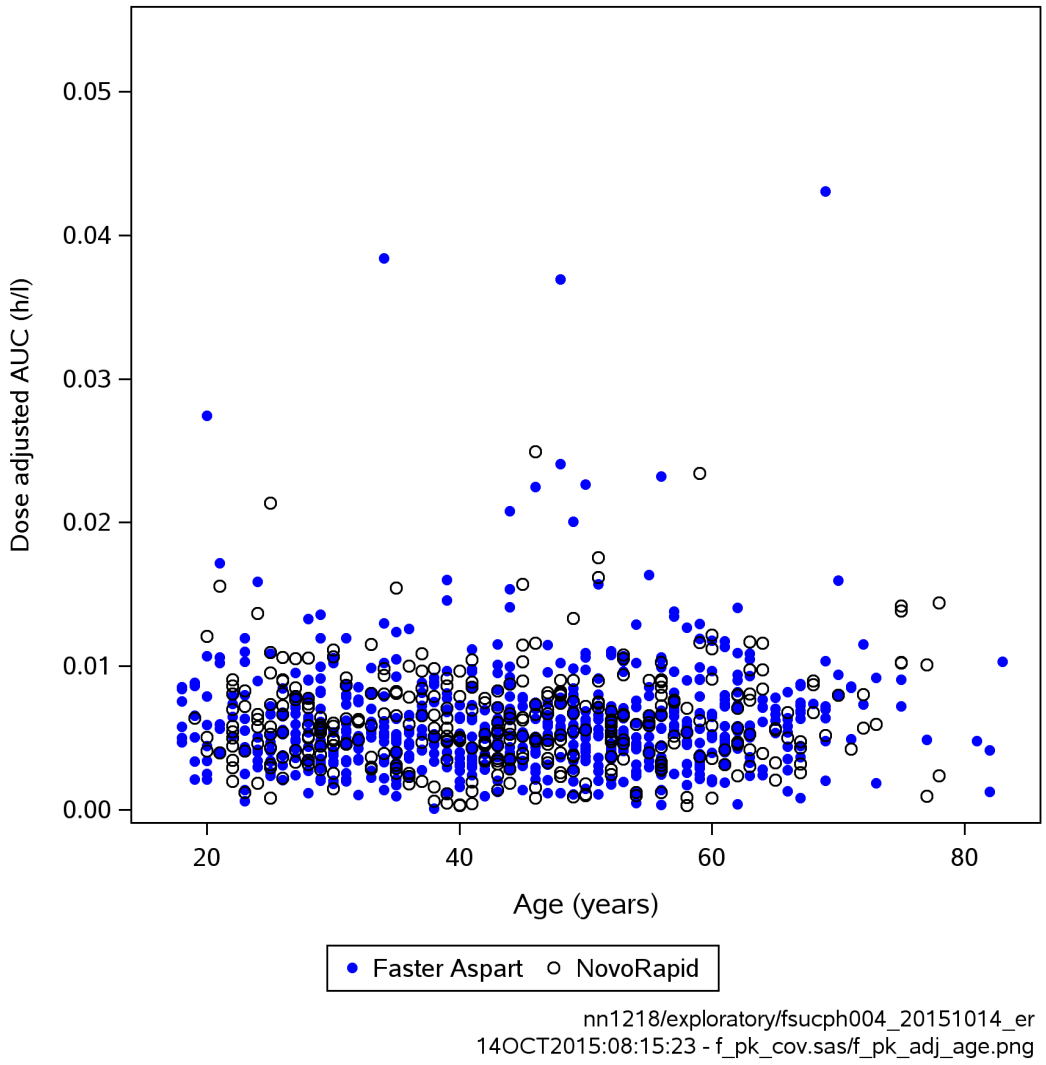
nn1218/exploratory/fsucph004_20151014_er
14OCT2015:08:13:23 - a_pk_age.sas/a_pk_age.txt

9: Linear regression of predicted dose adjusted IAsp AUC vs crcl - after meal-test (week 26) - phase 3 trial 3852 in T1DM patients - full analysis set

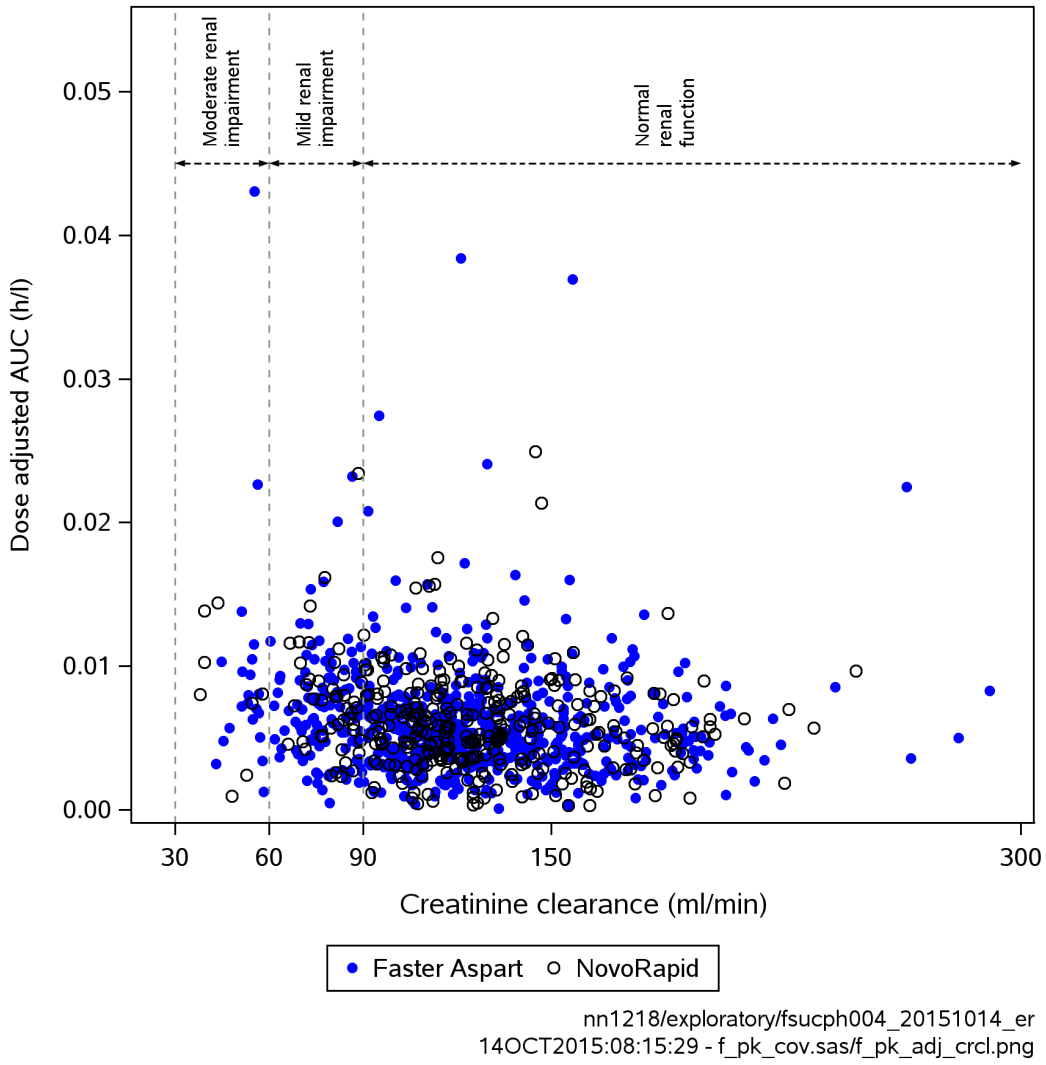
	Estimate	95% CI	P-value
Estimates			
FA - crcl slope	-0.31	[-0.46;-0.16]	<0.001
NR - crcl slope	-0.40	[-0.63;-0.18]	<0.001
FA - intercept	-5.27	[-5.31;-5.22]	
NR - intercept	-5.27	[-5.34;-5.21]	
Faster Aspart vs. NovoRapid			
Test for no treatment difference			0.772

CI: confidence interval.
The log-transformed endpoint was analysed using a linear regression on log-crcl with treatment-dependent intercept and slope
The Faster aspart group consists of subjects in Faster aspart (meal) arm or Faster aspart (post) arm.

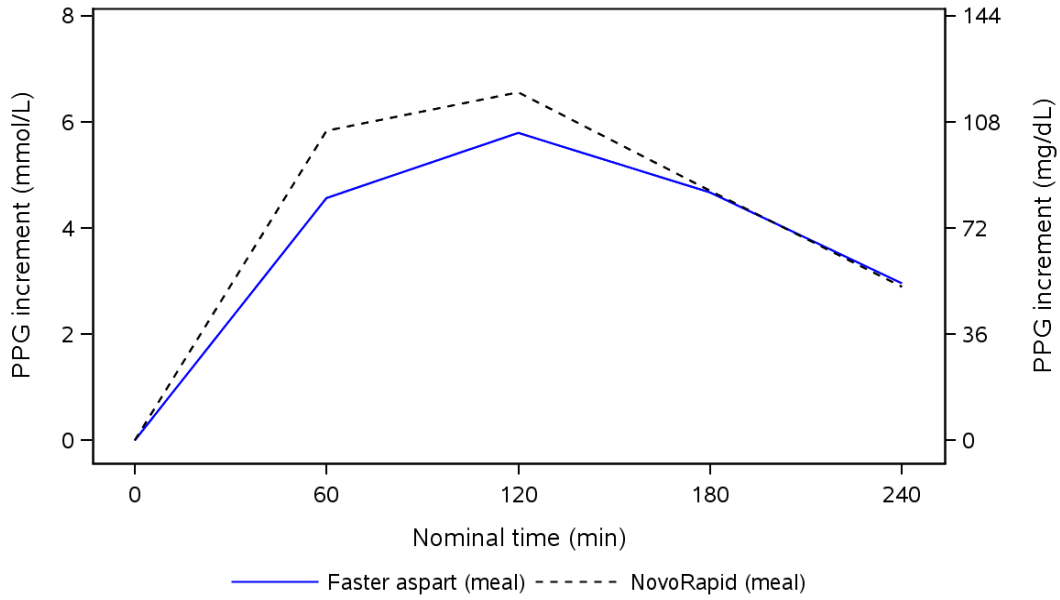
nn1218/exploratory/fsucph004_20151014_er
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10: Dose adjusted AUC vs age - trial 3852 in T1DM patients - FAS



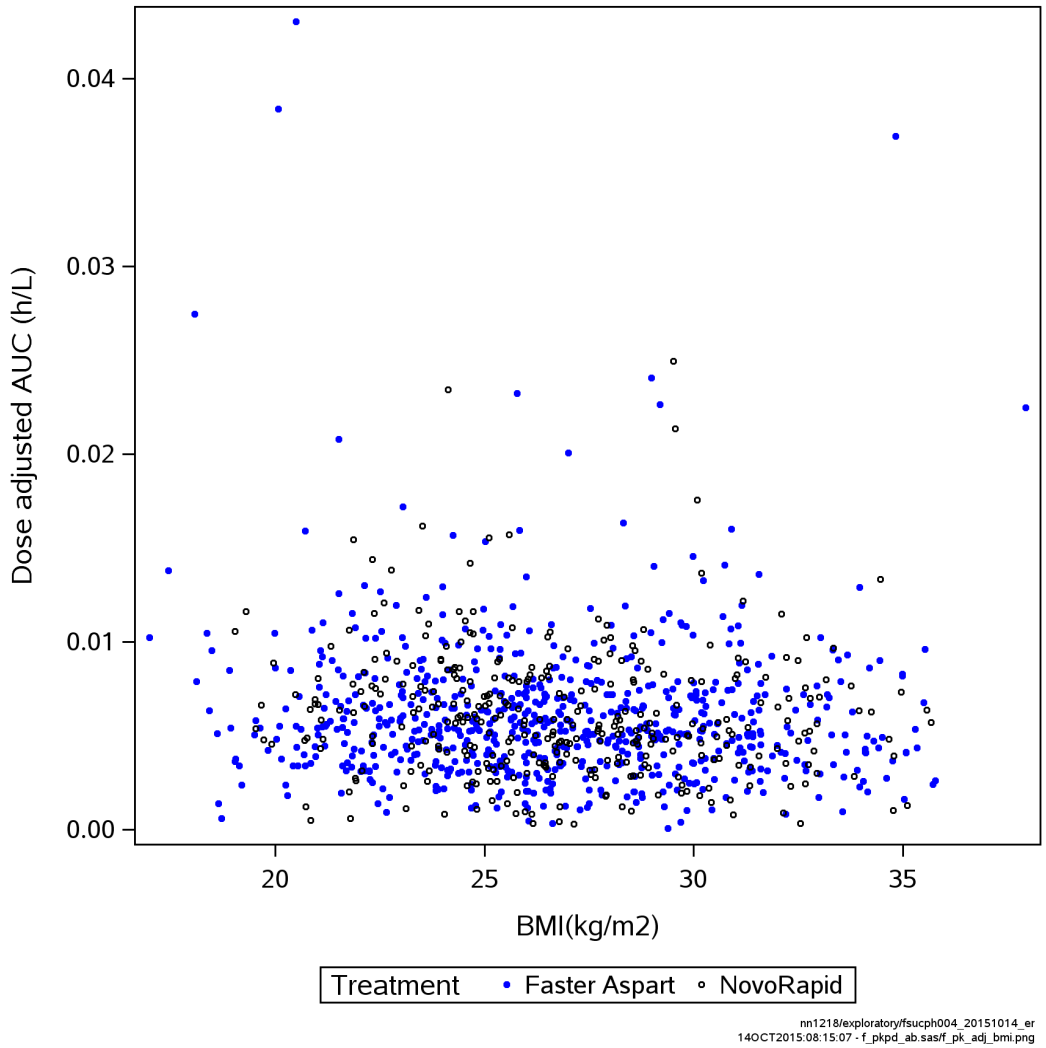
11: Dose adjusted AUC vs creatinine clearance - trial 3852 in T1DM patients - FAS



PPG: Postprandial glucose
Error bars: +/- Standard error (mean)
Observed data, except for cases where glucose or glucagon is administered. If glucose or glucagon is administered then the last measurement before rescue intervention will be carried forward.

nn1218/exploratory/fsucph004_20151014_er
14OCT2015:08:16:27 - f_ppg_inc_mean_wk_fas/f_ppg_inc_mean_W26_fas.png

12: Postprandial glucose increments (meal test) at week 26 - mean plot - phase 3 trial 3852 in T1DM patients - full analysis set



13: Dose adjusted AUC vs BMI - trial 3852 FAS with actual treatment

14: Insulin antibody level percentiles (week 26) - phase 3 trial 3852 in T1DM patients - full analysis set

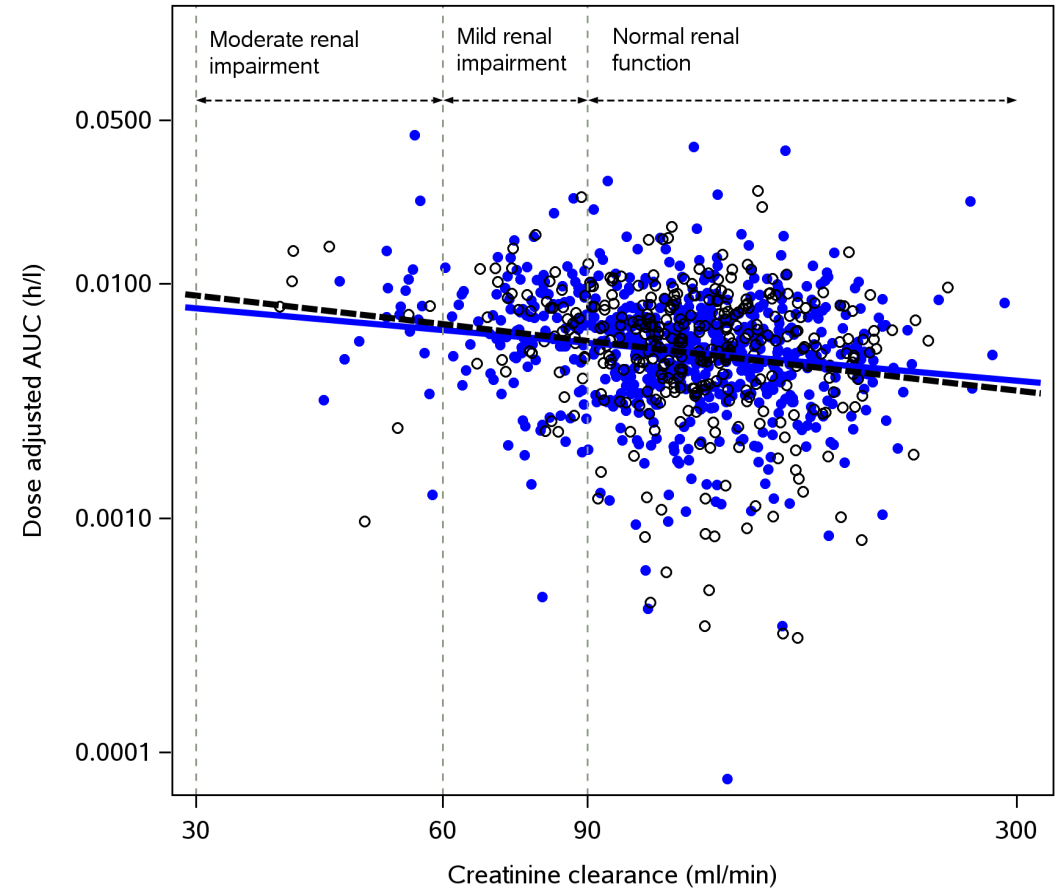
	Percentiles						
Assessment	Min	10th	25th	50th	75th	90th	Max
Total antibodies (% B/T)	0.17	2.41	5.97	13.07	24.57	43.27	89.83
Specific antibodies (% B/T)	-2.15	0.03	0.17	0.50	1.54	4.23	52.14
Cross-reacting antibodies (% B/T)	0.02	1.96	5.19	11.51	22.45	39.69	89.75

15: Subjects included in the PK analysis - age and actual treatment - phase 3 trial 3852 in T1DM patients - full analysis set

Group	Treatment	N
In total		1030
Treatment	Faster aspart (meal)	340
	Faster aspart (post)	342
	NovoRapid (meal)	348
Aged 18-35	In total	314
	Faster aspart (meal)	86
	Faster aspart (post)	118
	NovoRapid (meal)	110
Aged 36-45	In total	220
	Faster aspart (meal)	72
	Faster aspart (post)	63
	NovoRapid (meal)	85
Aged 46-55	In total	245
	Faster aspart (meal)	89
	Faster aspart (post)	82
	NovoRapid (meal)	74
Aged 56-65	In total	183
	Faster aspart (meal)	64
	Faster aspart (post)	63
	NovoRapid (meal)	56
Aged 66-75	In total	59
	Faster aspart (meal)	25
	Faster aspart (post)	15
	NovoRapid (meal)	19
Aged 76-85	In total	9
	Faster aspart (meal)	4
	Faster aspart (post)	1
	NovoRapid (meal)	4

16: Subjects included in the PK analysis - baseline characteristics - phase 3 trial 3852 in T1DM patients - full analysis set

Sex	Assessment	N	Min	Lower quartile	Median	Mean	Upper quartile	Max
Both	Age (years)	1030	18	33	45	45	55	83
	Weight (kg)	1030	45.3	68.8	78.8	80.1	90.7	140.0
	BMI	1030	17.0	24.0	26.5	26.7	29.5	37.9
Male	Age (years)	610	18	33	45	45	55	83
	Weight (kg)	610	53.6	76.2	85.8	86.5	95.1	140.0
	BMI	610	18.1	24.7	27.1	27.2	29.7	35.7
Female	Age (years)	420	18	33	45	44	56	82
	Weight (kg)	420	45.3	62.0	69.1	70.7	77.8	123.4
	BMI	420	17.0	23.0	25.6	26.0	28.8	37.9



17: Dose adjusted AUC vs creatinine clearance and linear fit plots by treatment - phase 3 trial 3852 in T1DM patients - FAS

フィアスプ注フレックスタッチ
フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

2.7.2.5. 付録
5. 総インスリン アスパルト濃度に基づく
薬物動態特性

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List of abbreviations and definitions of terms

$50\%C_{max}$	50% of maximum insulin aspart concentration
$50\%GIR_{max}$	50% of maximum glucose infusion rate
AUC	area under the curve
CI	confidence interval
C_{max}	maximum observed concentration
CV	coefficient of variation
Faster aspart	fast-acting insulin aspart
IAsp	insulin aspart
SD	single-dose
std	standard deviation
$t_{½}$	terminal half-life
T1DM	type 1 diabetes mellitus
t_{max}	time to maximum observed concentration
U	unit(s)
V_d	volume of distribution

1 Pharmacokinetic properties based on total insulin aspart concentration

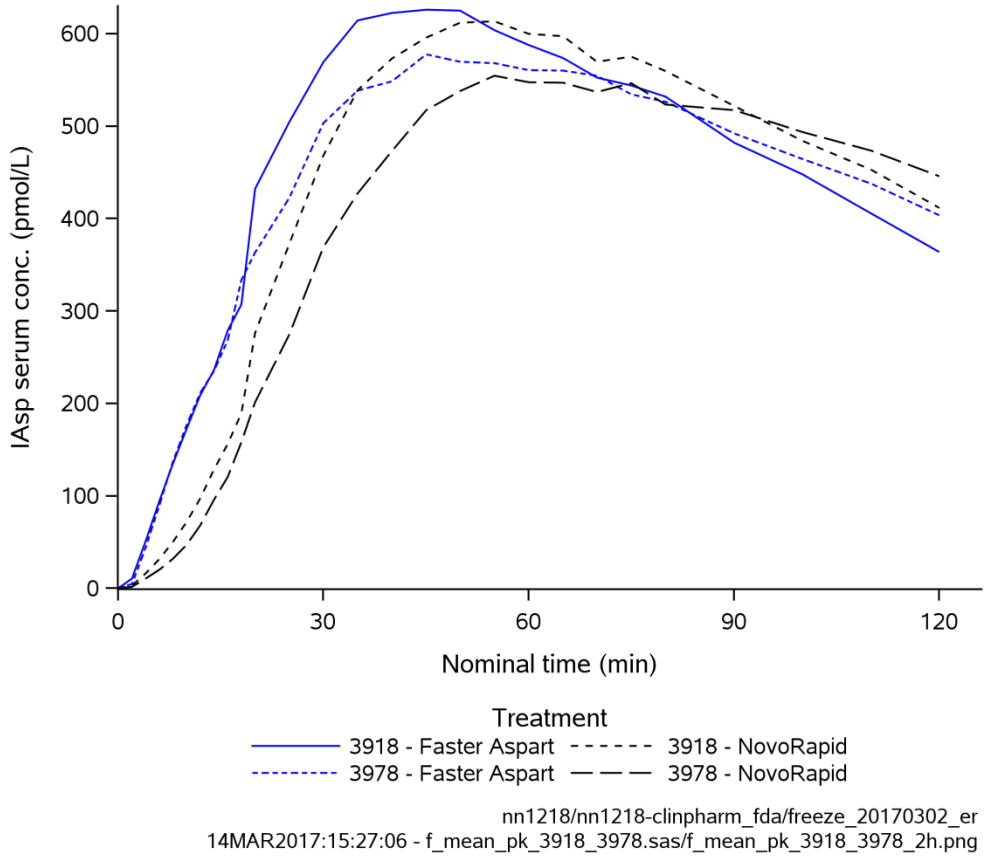
1.1 Pharmacokinetic treatment differences following single subcutaneous injection in Japanese adult subjects with T1DM

1.1.1 Treatment difference

Trial 3918 compared the pharmacokinetic and pharmacodynamic properties of faster aspart and NovoRapid® in Japanese subjects with T1DM following administration of a single dose (0.2 U/kg).

The design of trial 3918 replicated that of trial 3978 which compared the pharmacokinetic and pharmacodynamic properties of faster aspart and NovoRapid® in White subjects. In general, the design and methodology used was comparable across the studies.

In trial 3918 in Japanese subjects with T1DM, serum insulin aspart concentration-time curve of faster aspart showed a left shift compared to that of NovoRapid®, indicating a faster onset of exposure and increased initial absorption rate resulting in more insulin being available earlier in Japanese subjects, as also seen in White subjects (Figure 1–1).



Cross-reference: Appendix 5.6, Figure 11

Figure 1–1 Mean insulin aspart profiles (0-2 hours) with faster aspart and NovoRapid® in Japanese (trial 3918) and White (trial 3978) subjects with T1DM

As indicated by the concentration-time curves (Figure 1–1), a faster onset of exposure (assessed using onset of appearance, time to 50%$C_{max,IAsp}$ and t_{max}) was seen with faster aspart than with NovoRapid® in Japanese subjects, as was also observed in White subjects (Table 1–1). As was the case for White subjects, the estimated onset of appearance of faster aspart in Japanese subjects was approximately twice as fast (by 2.3 minutes) as with NovoRapid®. Likewise, the estimated time to 50% $C_{max,IAsp}$ for faster aspart in Japanese subjects was significantly earlier (by 7.3 minutes) than for NovoRapid®. Finally, $t_{max,IAsp}$ in Japanese subjects was also significantly earlier for faster aspart than for NovoRapid®.

Table 1–1 Treatment differences and 95% CI for onset of insulin exposure in Japanese (trial 3918) and White (trial 3978) adult subjects with T1DM

		Japanese (3918)	White (3978)
Onset of Appearance [a] (min), mean	Faster aspart	2.37	2.53
	NovoRapid®	4.65	5.24
	Treatment difference [95% CI]	-2.28 [-2.82;-1.74]	-2.71 [-3.26;-2.16]
Time to 50% $C_{max,IAsp}$ (min), mean	Faster aspart	20.07	20.78
	NovoRapid®	27.32	30.86
	Treatment difference[95% CI]	-7.25 [-9.23;-5.26]	-10.08 [-12.41;-7.75]
$t_{max,IAsp}$ (min), mean	Faster aspart	49.67	63.04
	NovoRapid®	63.60	73.46
	Treatment difference [95% CI]	-13.93 [-21.46;-6.40]	-10.42 [-18.52;-2.31]

Number of subjects: Trial **3918**; Faster aspart = 41 subjects, NovoRapid® = 41 subjects; Trial **3978**; Faster aspart = 51 subjects, NovoRapid® = 51 subjects. [a] Defined as time to first time above 10 pmol/L

Cross-reference: Appendix 5.6. Tables 7, 8, 13 and 14

Early insulin exposure was significantly larger for faster aspart than for NovoRapid® over the first 90 minutes in Japanese subjects, as was also seen in White subjects (Table 1–2). E.g., insulin aspart exposure during the first 30 minutes after administration ($AUC_{IAsp,0\text{-}30min}$) was approximately twice as large for faster aspart than for NovoRapid® in both populations.

Table 1–2 Treatment ratios and 95% CI for early insulin exposure in Japanese (trial 3918) and White (trial 3978) adult subjects with T1DM

	Treatment Ratio [95% CI] Faster aspart/ NovoRapid®				
Trial	$AUC_{IAsp,0\text{-}15min}$	$AUC_{IAsp,0\text{-}30min}$	$AUC_{IAsp,0\text{-}1hour}$	$AUC_{IAsp,0\text{-}90min}$	$AUC_{IAsp,0\text{-}2hours}$
Japanese (3918)	2.68 [2.25; 3.19]	1.74 [1.51; 1.99]	1.25 [1.12; 1.38]	1.12 [1.02;1.22]	1.06 [0.98;1.15]
White (3978)	3.55 [2.92; 4.31]	1.92 [1.68; 2.21]	1.28 [1.16; 1.42]	1.14 [1.04;1.26]	1.07 [0.97;1.18]

Number of subjects: Trial **3918**; Faster aspart = 41 subjects, NovoRapid® = 41 subjects; Trial **3978**; Faster aspart = 51 subjects, NovoRapid® = 51 subjects.

Cross-reference: Appendix 5.6, Tables 15 and 16

Total exposure ($AUC_{IAsp,0\text{-}12h}$) and maximum concentration ($C_{max,IAsp}$) were similar for faster aspart and NovoRapid® in Japanese subjects, as was also observed in White subjects (Table 1–3).

Table 1–3 Treatment ratios and 95% CI for total insulin exposure and maximum insulin concentration in Japanese (trial 3918) and White (trial 3978) adult subjects with T1DM

		Japanese (3918)	White (3978)
$AUC_{IAsp,\ 0\text{-}12hour}$ (pmol*h/L)	Faster aspart	1341.86	1502.33
	NovoRapid®	1382.34	1526.42
	Treatment ratio [95% CI]*	0.97 [0.94;1.00]	0.98 [0.89; 1.09]
$C_{max,IAsp}$ (pmol/L)	Faster aspart	634.71	607.77
	NovoRapid®	623.18	597.72
	Treatment ratio [95% CI]	1.02 [0.93; 1.12]	1.02 [0.93; 1.11]

*p=0.067

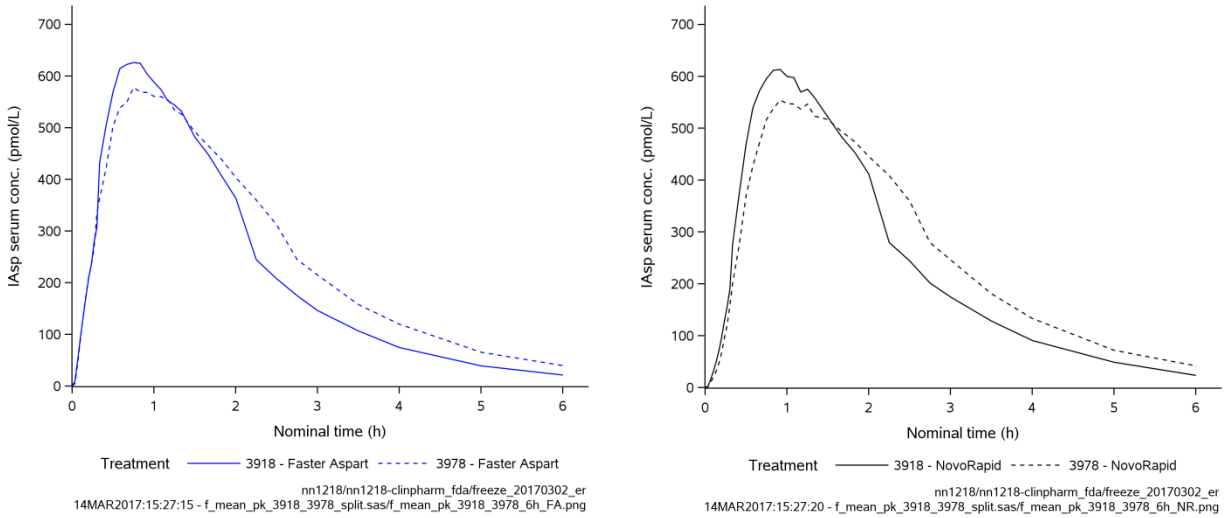
Number of subjects: Trial **3918**; Faster aspart = 41 subjects, NovoRapid® = 41 subjects; Trial **3978**; Faster aspart = 51 subjects, NovoRapid® = 51 subjects.

Cross-reference: Appendix 5.6, Tables 15 and 16

In conclusion, the greater early exposure for faster aspart compared to NovoRapid® observed in White subjects with T1DM is preserved in Japanese subjects with T1DM and overall total exposure and maximum concentration seemed to be comparable for faster aspart and NovoRapid® for both populations.

1.1.2 Japanese versus White subjects with T1DM

Overall, the insulin concentration-time profiles for faster aspart were comparable between Japanese (trial 3918) and White (trial 3978) subjects, as was observed for NovoRapid® (Figure 1–2).



Cross-reference: Appendix 5.6, Figures 17 and 18

Figure 1–2 Mean insulin aspart profiles (0-6 hours) in Japanese (trial 3918) and White (trial 3978) subjects with T1DM for faster aspart (left) and NovoRapid® (right)

The median terminal half-life ($t_{½}$) after subcutaneous administration of faster aspart was 57 minutes in Japanese subjects in trial 3918 (Appendix 5.6, Table 19) compared to 66 minutes in White subjects in trial 3978 (Trial 3978 (M 5.3.4.2), EOT Table 14.2.55).

Based on trials 3918 and 3978, only minor differences were observed for total insulin aspart exposure ($AUC_{IAsp,0-12h}$) and maximum insulin aspart concentration ($C_{max,IAsp}$) between Japanese and White subjects for faster aspart as well as for NovoRapid® (Table 1–3).

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フィアスプ注ペンフィル
フィアスプ注 100 単位/mL

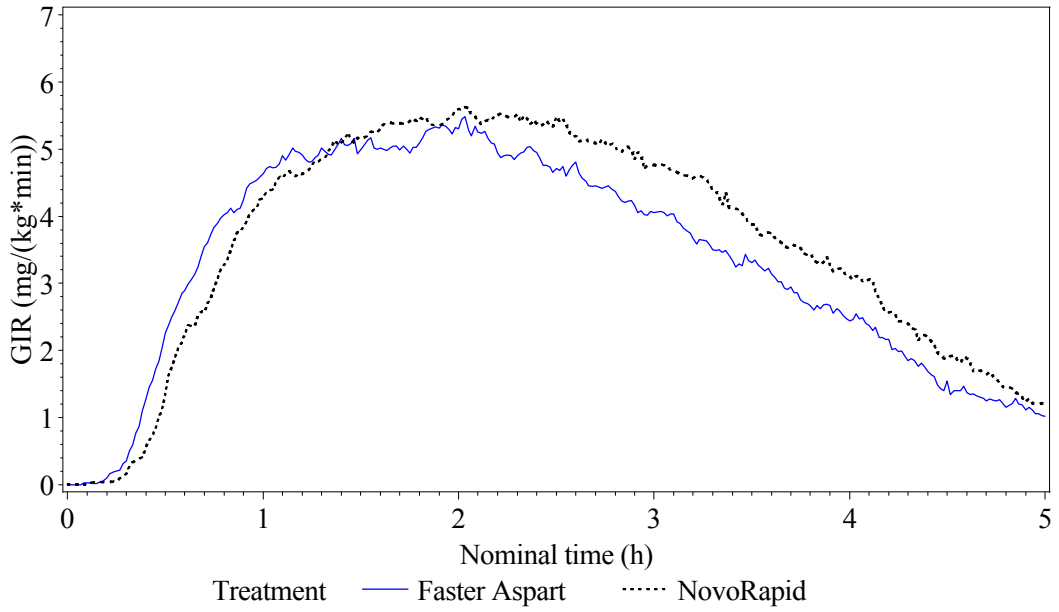
2.7.2.5. 付録
6. 3918 試験の結果に基づく図表

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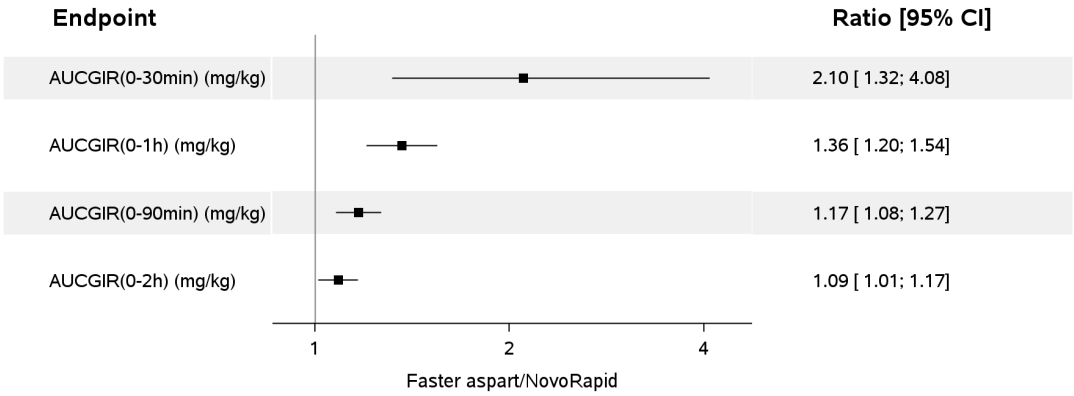
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nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:18 - f_mean_gir.sas/f_mean_gir_0_5h.cgm

1: GIR - mean profiles - full analysis set - trial 3918



The endpoint for AUCGIR(0-30 min) was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fiellers method.
The other endpoints were log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect.

nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:20 - f_pd_gir_auc_forest.sas/f_pd_gir_auc_forest.png

2: GIR - AUCGIR - forest plot of statistical analyses - full analysis set - trial 3918

3: GIR - AUCGIR(2-12h) - statistical analysis - full analysis set - trial 3918

	N	Estimate	SE	95% CI	P-value
AUCGIR(2-12h)(mg/kg)					
LSMeans					
Faster Aspart	43	591.96	0.06		
NovoRapid	42	701.66	0.06		
Treatment Ratio					
Faster Aspart / NovoRapid		0.84		[0.77;0.93]	<0.001

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect

nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:08 - a_pd_gir_auc_2_12.sas/a_pd_gir_auc_2_12.txt

4: GIR - Time to late 50% GIRmax - statistical analysis - full analysis set - trial 3918

	N	Estimate	SE	95% CI	P-value
Time to late 50% GIRmax (min)					
LSMeans					
Faster Aspart	43	239.16	7.20		
NovoRapid	42	251.31	7.27		
Treatment Difference					
Faster Aspart - NovoRapid		-12.15		[-26.33;2.02]	0.091
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.95		[0.90;1.01]	

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method

nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:09 - a_pd_gir_time_to_50_girmax.sas/a_pd_gir_time_to_50_girmax.txt

5: Insulin Aspart - AUC(2-12h) - statistical analysis - full analysis set - trial 3918

	N	Estimate	95% CI	P-value
AUCIASP(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart	41	197.51		
NovoRapid	41	225.37		
Treatment Ratio				
Faster Aspart / NovoRapid		0.88	[0.77;1.00]	0.049

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect.

nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:15 - a_pk_free_iasp_auc_2_12.sas/a_pk_free_iasp_auc_2_12.txt

6: Insulin Aspart - Time to late 50% Cmax - statistical analysis - full analysis set - trial 3918

	N	Estimate	SE	95% CI	P-value
Time to late 50% Cmax (min)					
LSMeans					
Faster Aspart	41	131.09	7.13		
NovoRapid	41	155.48	7.13		
Treatment Difference					
Faster Aspart - NovoRapid		-24.39		[-37.82;-10.97]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.84		[0.77;0.93]	

N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.
nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:11 - a_pk_add_fi.sas/a_pk_free_last_time_to_50_Cmax.txt

7: Total insulin Aspart - Time to 50% Cmax - statistical analysis - full analysis set - trial 3918

	N	Estimate	SE	95% CI	P-value
Time to 50% Cmax (min)					
LSMeans					
Faster Aspart	41	20.07	0.85		
NovoRapid	41	27.32	0.85		
Treatment Difference					
Faster Aspart - NovoRapid		-7.25		[-9.23;-5.26]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.73		[0.67;0.80]	

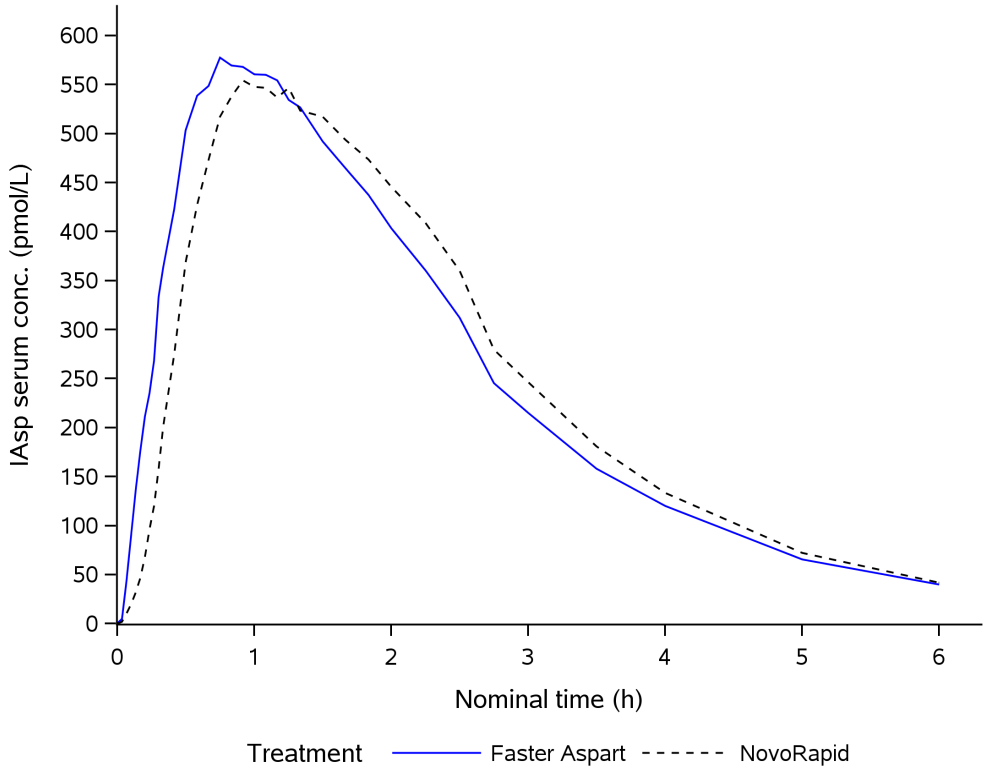
N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.
nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:11 - a_pk_add_fi.sas/a_pk_total_time_to_50_Cmax.txt

8: Total Insulin Aspart - Time to 50% Cmax - statistical analysis - trial 3978

	N	Estimate	SE	95% CI	P-value
Time to 50% Cmax (min)					
LSMeans					
FIA (Q)	51	20.78	0.95		
NovoRapid	51	30.86	0.95		
Treatment Difference					
FIA (Q) - NovoRapid		-10.08		[-12.41;-7.75]	<0.001
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.67		[0.61;0.74]	

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method

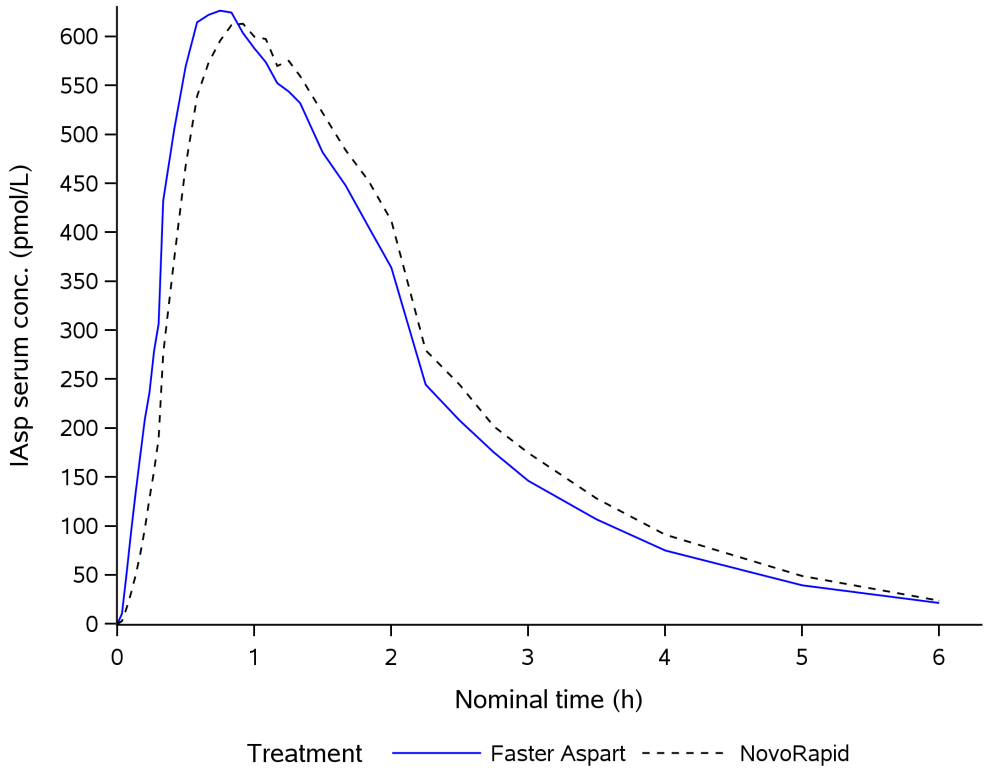
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25JUN2018:17:31:14 - a_pk_add_fi_3978.sas/a_pk_add_fi_3978.txt



IAsp is total insulin aspart

nn1218/nn1218-clinpharm_fda/freeze_20170302_er
14MAR2017:15:27:01 - f_mean_pk.sas/f_mean_pk_3978_6h.png

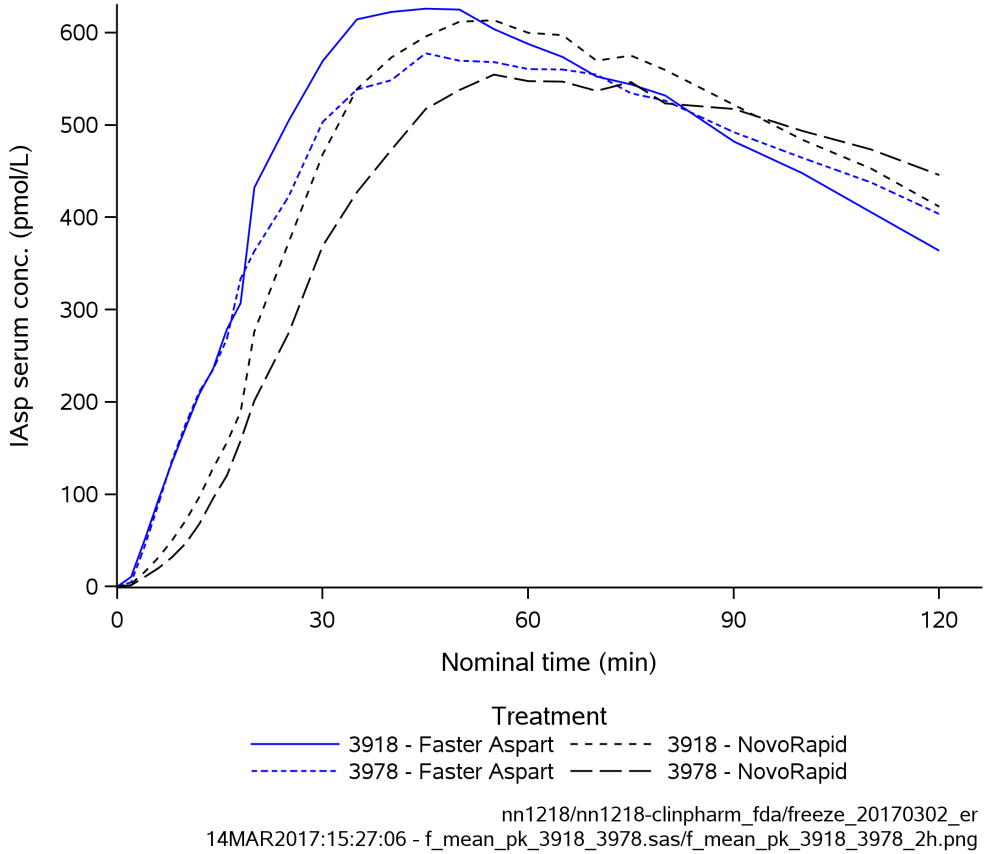
9: Total Insulin Aspart - mean profiles (0-6h) - adults, 0.2 U/kg, trial 3978



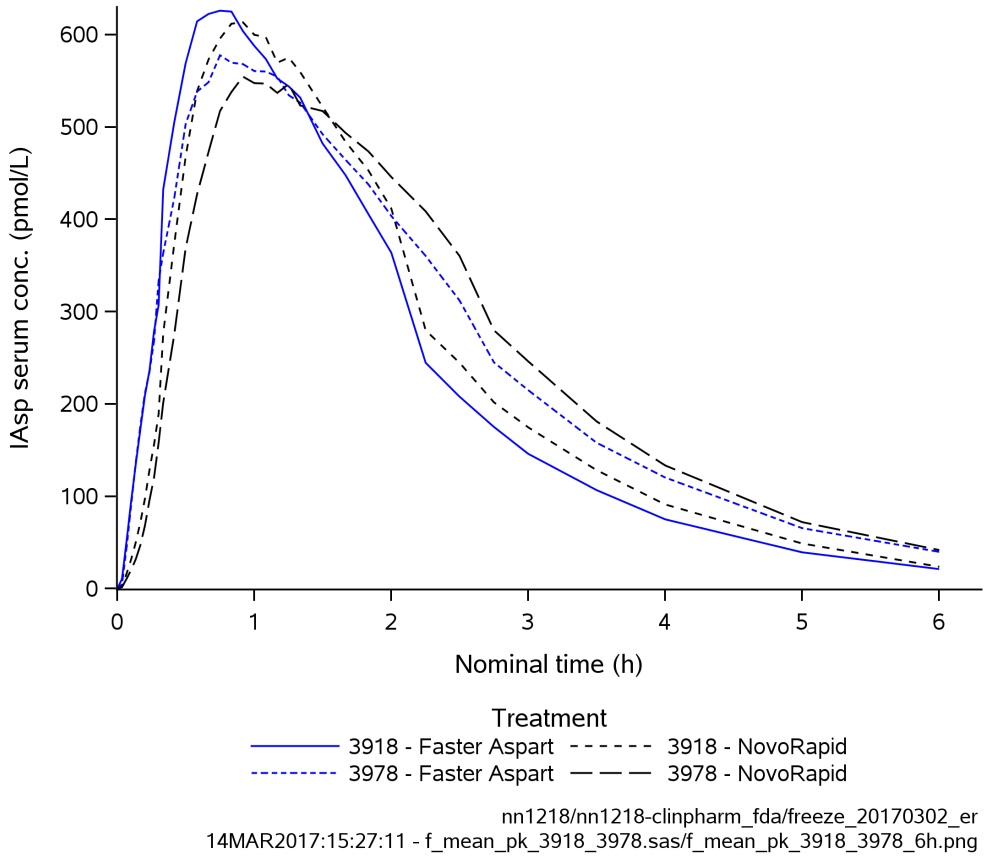
IAsp is total insulin aspart

nn1218/nn1218-clinpharm_fda/freeze_20170302_er
14MAR2017:15:27:02 - f_mean_pk.sas/f_mean_pk_3918_6h.png

10: Total Insulin Aspart - mean profiles (0-6h) - trial 3918



11: Total Insulin Aspart - mean profiles - 0.2 U/kg, trials 3918 and 3978



12: Total Insulin Aspart - mean profiles - 0.2 U/kg, trials 3918 and 3978

13: Total Insulin Aspart endpoints - time parameters - statistical analysis - trial 3978

	N	Estimate	SE	95% CI	P-value
Onset of appearance (min)					
LSMeans					
FIA (Q)	51	2.53	0.21		
NovoRapid	51	5.24	0.21		
Treatment Difference					
FIA (Q) - NovoRapid		-2.71		[-3.26;-2.16]	<0.001
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.48		[0.40;0.57]	
tmax (min)					
LSMeans					
FIA (Q)	51	63.04	3.74		
NovoRapid	51	73.46	3.74		
Treatment Difference					
FIA (Q) - NovoRapid		-10.42		[-18.52;-2.31]	0.012
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.86		[0.76;0.97]	
Time to late 50% Cmax (min)					
LSMeans					
FIA (Q)	51	155.84	6.68		
NovoRapid	51	168.49	6.68		
Treatment Difference					
FIA (Q) - NovoRapid		-12.65		[-26.41;1.12]	0.071
Fieller Treatment Ratio					
FIA (Q) / NovoRapid		0.92		[0.85;1.01]	

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method

nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:16 - a_pkpd_add_fi_3978.sas/a_pk_ad_fi_3978.txt

14: Total Insulin Aspart endpoint - Time parameters - statistical analysis - trial 3918 full analysis set

	N	Estimate	SE	95% CI	P-value
Onset of appearance (min)					
LSMeans					
Faster Aspart	41	2.37	0.22		
NovoRapid	41	4.65	0.22		
Treatment Difference					
Faster Aspart - NovoRapid		-2.28		[-2.82;-1.74]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.51		[0.42;0.61]	
tmax (min)					
LSMeans					
Faster Aspart	41	49.67	3.24		
NovoRapid	41	63.60	3.24		
Treatment Difference					
Faster Aspart - NovoRapid		-13.93		[-21.46;-6.40]	<0.001
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.78		[0.68;0.89]	
Time to late 50% Cmax (min)					
LSMeans					
Faster Aspart	41	127.18	5.77		
NovoRapid	41	145.68	5.77		
Treatment Difference					
Faster Aspart - NovoRapid		-18.50		[-30.39;-6.61]	0.003
Fieller Treatment Ratio					
Faster Aspart / NovoRapid		0.87		[0.80;0.95]	

N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error
Endpoint was analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect. Ratios and the corresponding CIs were estimated using Fieller's method.

nn1218/exploratory/fotcph004_20180327_er
25JUN2018:17:31:12 - a_pk_add_fi_3918.sas/a_pk_add_fi_3918.txt

15: Total Insulin Aspart endpoints - AUCs and Cmax - Statistical Analysis - trial 3978 - full analysis set

	N	Estimate	SE	95% CI	P-value
AUCIASP(0-15min)(h*pmol/L)					
LSMeans					
FIA (Q)	51	26.09	0.08		
NovoRapid	51	7.36	0.08		
Treatment Ratio					
FIA(Q) / NovoRapid		3.55		[2.92;4.31]	<0.001
AUCIASP(0-30min)(h*pmol/L)					
LSMeans					
FIA (Q)	51	113.96	0.07		
NovoRapid	51	59.24	0.07		
Treatment Ratio					
FIA(Q) / NovoRapid		1.92		[1.68;2.21]	<0.001
AUCIASP(0-1h)(h*pmol/L)					
LSMeans					
FIA (Q)	51	374.29	0.06		
NovoRapid	51	291.71	0.06		
Treatment Ratio					
FIA(Q) / NovoRapid		1.28		[1.16;1.42]	<0.001
AUCIASP(0-90min)(h*pmol/L)					
LSMeans					
FIA (Q)	51	630.05	0.05		
NovoRapid	51	552.36	0.05		
Treatment Ratio					
FIA(Q) / NovoRapid		1.14		[1.04;1.26]	0.008
AUCIASP(0-2h)(h*pmol/L)					
LSMeans					
FIA (Q)	51	847.05	0.05		
NovoRapid	51	790.11	0.05		
Treatment Ratio					
FIA(Q) / NovoRapid		1.07		[0.97;1.18]	0.157
AUCIASP(0-12h)(h*pmol/L)					
LSMeans					
FIA (Q)	51	1502.33	0.06		
NovoRapid	51	1526.42	0.06		
Treatment Ratio					
FIA(Q) / NovoRapid		0.98		[0.89;1.09]	0.762
AUCIASP(2-12h)(h*pmol/L)					
LSMeans					
FIA (Q)	51	578.67	0.11		
NovoRapid	51	673.12	0.11		
Treatment Ratio					
FIA(Q) / NovoRapid		0.86		[0.70;1.06]	0.153
Cmax (pmol/L)					
LSMeans					
FIA (Q)	51	607.77	0.05		
NovoRapid	51	597.72	0.05		
Treatment Ratio					
FIA(Q) / NovoRapid		1.02		[0.93;1.11]	0.710

N: Number of subjects contributing to analysis, CI: Confidence Interval, SE: Standard Error
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect

nn1218/nn1218-clinpharm_fda/freeze_20170302_er

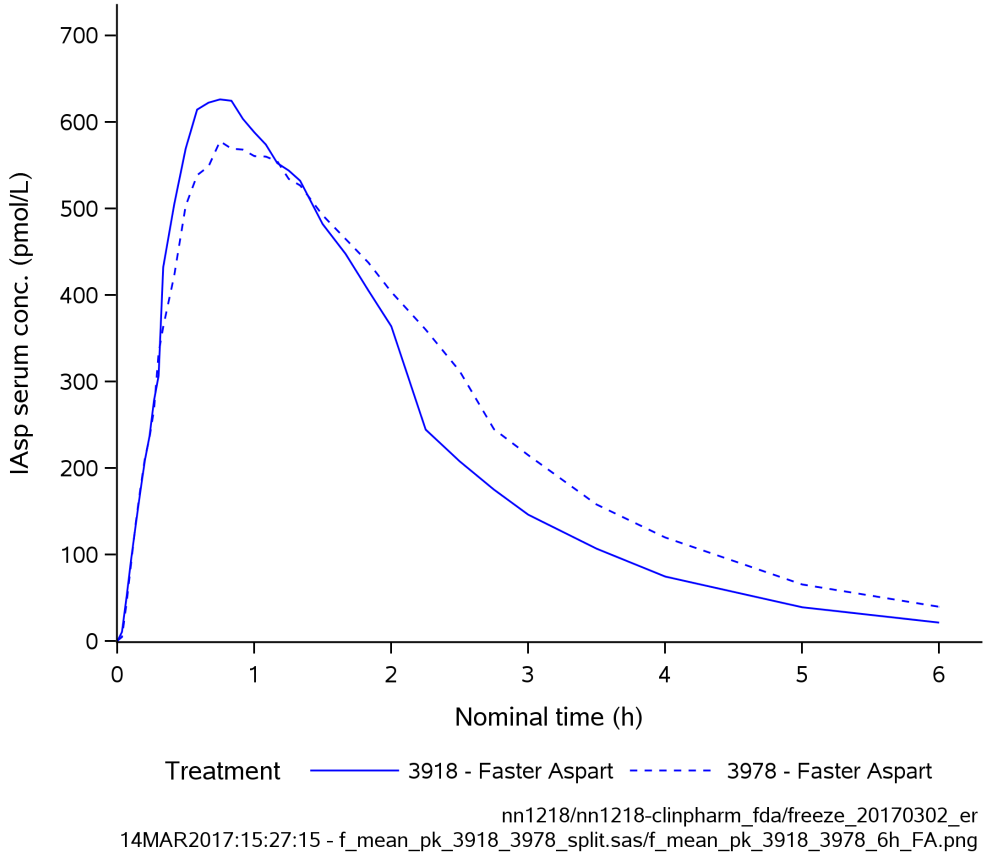
14MAR2017:15:25:04 - a_pkpd_log_3978.sas/a_pk_log_3978.txt

16: Total Insulin Aspart endpoints - AUCs and Cmax - statistical analysis - trial 3918, full analysis set

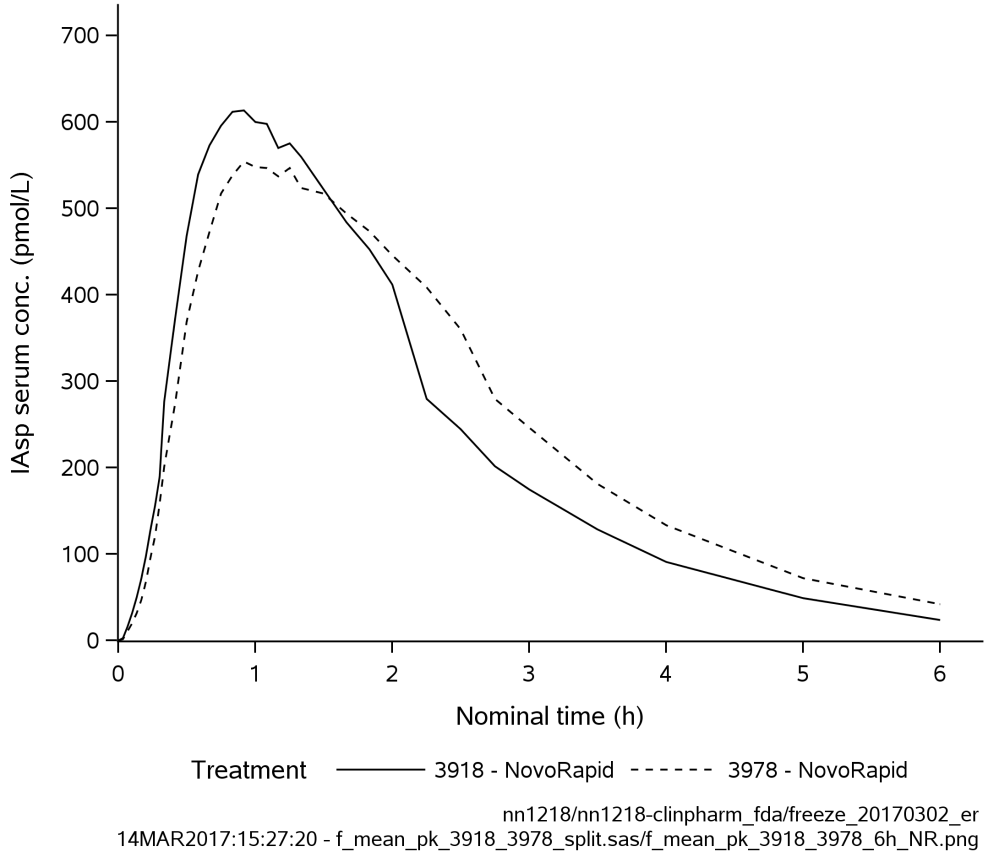
	N	Estimate	95% CI	P-value
AUCIASP(0-15min)(h*pmol/L)				
LSMeans				
Faster Aspart	41	27.87		
NovoRapid	41	10.42		
Treatment Ratio				
Faster Aspart / NovoRapid		2.68	[2.25;3.19]	<0.001
AUCIASP(0-30min)(h*pmol/L)				
LSMeans				
Faster Aspart	41	130.43		
NovoRapid	41	75.17		
Treatment Ratio				
Faster Aspart / NovoRapid		1.74	[1.51;1.99]	<0.001
AUCIASP(0-1h)(h*pmol/L)				
LSMeans				
Faster Aspart	41	420.34		
NovoRapid	41	337.59		
Treatment Ratio				
Faster Aspart / NovoRapid		1.25	[1.12;1.38]	<0.001
AUCIASP(0-90min)(h*pmol/L)				
LSMeans				
Faster Aspart	41	681.51		
NovoRapid	41	609.04		
Treatment Ratio				
Faster Aspart / NovoRapid		1.12	[1.02;1.22]	0.016
AUCIASP(0-2h)(h*pmol/L)				
LSMeans				
Faster Aspart	41	890.52		
NovoRapid	41	839.08		
Treatment Ratio				
Faster Aspart / NovoRapid		1.06	[0.98;1.15]	0.134
AUCIASP(0-12h)(h*pmol/L)				
LSMeans				
Faster Aspart	41	1341.86		
NovoRapid	41	1382.34		
Treatment Ratio				
Faster Aspart / NovoRapid		0.97	[0.94;1.00]	0.067
AUCIASP(2-12h)(h*pmol/L)				
LSMeans				
Faster Aspart	41	402.16		
NovoRapid	41	473.65		
Treatment Ratio				
Faster Aspart / NovoRapid		0.85	[0.75;0.96]	0.010
Cmax (pmol/L)				
LSMeans				
Faster Aspart	41	634.71		
NovoRapid	41	623.18		
Treatment Ratio				
Faster Aspart / NovoRapid		1.02	[0.93;1.12]	0.695

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint was log-transformed and analysed using a linear mixed model with treatment and period as fixed effects and subject as a random effect.

nn1218/nn1218-clinpharm_fda/freeze_20170302_er
14MAR2017:15:24:31 - a_pk_log_3918.sas/a_pk_log_3918.txt



17: Total Insulin Aspart - mean profiles (0-6 hours) - trials 3918 and 3978 - Faster Aspart



18: Total Insulin Aspart - mean profiles (0-6 hours) - trials 3918 and 3978 - NovoRapid

19: Total Insulin Aspart endpoints - descriptive statistics - trial 3918 - full analysis set

	Faster Aspart	NovoRapid
AUC(0-15min) (pmol*h/L)		
N	41	41
Mean (StD)	30.30 (13.44)	13.27 (9.36)
Median	28.05	12.01
Geometric mean (CV)	27.84 (44.36)	10.43 (70.51)
Min;Max	9.00; 80.52	2.66; 40.97
AUC(0-30min) (pmol*h/L)		
N	41	41
Mean (StD)	140.66 (56.86)	91.37 (55.08)
Median	127.40	77.01
Geometric mean (CV)	130.22 (40.43)	75.47 (60.28)
Min;Max	47.68; 293.67	22.38; 215.09
AUC(0-1h) (pmol*h/L)		
N	41	41
Mean (StD)	446.57 (160.69)	380.23 (180.43)
Median	406.28	331.45
Geometric mean (CV)	420.00 (35.98)	338.93 (47.45)
Min;Max	207.84; 882.90	122.86; 824.24
AUCIASP(0-90min) (h*pmol/L)		
N	41	41
Mean (StD)	717.04 (243.28)	664.04 (272.15)
Median	669.74	596.14
Geometric mean (CV)	681.16 (33.93)	610.90 (40.98)
Min;Max	359.66; 1544.94	267.27; 1466.29
AUC(0-2h) (pmol*h/L)		
N	41	41
Mean (StD)	929.89 (294.91)	898.04 (333.79)
Median	878.71	818.37
Geometric mean (CV)	890.60 (31.71)	841.30 (37.17)
Min;Max	498.06; 1955.91	421.84; 2001.44
AUC(0-12h) (pmol*h/L)		
N	41	41
Mean (StD)	1391.79 (427.37)	1436.90 (455.15)
Median	1283.76	1375.72
Geometric mean (CV)	1344.05 (30.71)	1384.73 (31.68)
Min;Max	949.07; 3046.92	951.66; 3258.54
AUC(0-inf) (pmol*h/L)		
N	41	41
Mean (StD)	1395.07 (429.96)	1440.63 (460.96)
Median	1283.77	1375.72
Geometric mean (CV)	1346.82 (30.82)	1387.46 (32.00)
Min;Max	949.07; 3054.99	951.69; 3266.45
Cmax (pmol/L)		
N	41	41
Mean (StD)	675.96 (249.68)	673.85 (264.27)
Median	616.90	658.30
Geometric mean (CV)	636.00 (36.94)	625.18 (39.22)
Min;Max	317.80; 1515.00	299.20; 1417.00
tmax (min)		
N	41	41
Mean (StD)	49.76 (17.82)	63.54 (23.27)
Median	50.00	60.00
Geometric mean (CV)	47.00 (35.81)	59.72 (36.63)

Total Insulin Aspart endpoints - descriptive statistics - trial 3918 - full analysis set

	Faster Aspart	NovoRapid
Min;Max	25.00; 100.00	35.00; 120.00
Onset of appearance (min)		
N	41	41
Mean (StD)	2.38 (0.83)	4.65 (1.88)
Median	2.18	4.38
Geometric mean (CV)	2.24 (34.79)	4.28 (40.33)
Min;Max	0.90; 5.07	2.00; 8.97
t1/2 (min)		
N	41	41
Mean (StD)	65.08 (32.90)	59.46 (28.61)
Median	56.86	50.80
Geometric mean (CV)	58.74 (50.54)	54.16 (48.12)
Min;Max	22.54; 203.53	27.52; 154.37

StD: standard deviation, CV: Coefficient of variation

nn1218/exploratory/fotcph004_20180327_er
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