

## Supplemental materials

**Supplemental Table S1** – Clinical characteristics of subjects studied at randomization

**Supplemental Table S2** - Outcome measures after three months of treatment

**Supplemental Table S3** – Endogenous glucose production, glucagon, and metabolites in the Gla-300 and Deg-100 studies

**Supplemental Figure S1** – Design of study (upper panel A) and clamp experiments (bottom panel B)

**Supplemental Figure S2** – Insulin concentrations of Gla-300 (serum free insulin) and Deg-100 (plasma total, i.e. bound+free), and glucose infusion rates (GIR) every 6 h

**Supplemental Figure S3** – Individual GIR and PG profiles during the euglycemic clamp studies (Gla-300 solid line, Deg-100 broken line)

**Supplemental Figure S4** - Plasma glucagon, plasma free fatty acids, blood glycerol and  $\beta$ -hydroxybutyrate concentrations in the Gla-300 and Deg-100 studies

**Supplemental Figure S5** –Blood lactate and alanine concentrations in the Gla-300 and Deg-100 studies.

Supplemental Table 1

N	22
Gender	11F, 11M
Age (years)	44.3 ± 12.4
BMI (kg/m <sup>2</sup> )	22.5 ± 2.7
Diabetes duration (years)	25.5 ± 11.7
Plasma C-peptide (ng/ml)	0.02 ± 0.01
HbA1c (%)	7.07 ± 0.63
HbA1c, mmol/mol (IFCC)	53.7 ± 6.9
Basal daily insulin dose (U/kg)*	0.27 ± 0.06
Total daily insulin dose (U/kg)	0.58 ± 0.13

\*Insulin glargine 100U/ml

Supplemental Table 2

	<b><u>After three months of treatment</u></b>		
	<b>Gla-300</b>	<b>Deg-100</b>	<b>Between-treatment <i>p value</i></b>
HbA1c (%)	6.88±0.55	6.86±0.52	0.812
HbA1c, mmol/mol (IFCC)	51.6±6.0	51.4±5.6	0.812
Basal daily insulin dose (U/kg)	0.34 ± 0.08	0.26 ± 0.06	<0.001
Total daily insulin dose (U/kg)	0.64 ± 0.13	0.51 ± 0.10	<0.001
Hypoglycemia rate before the clamp studies*	--	--	

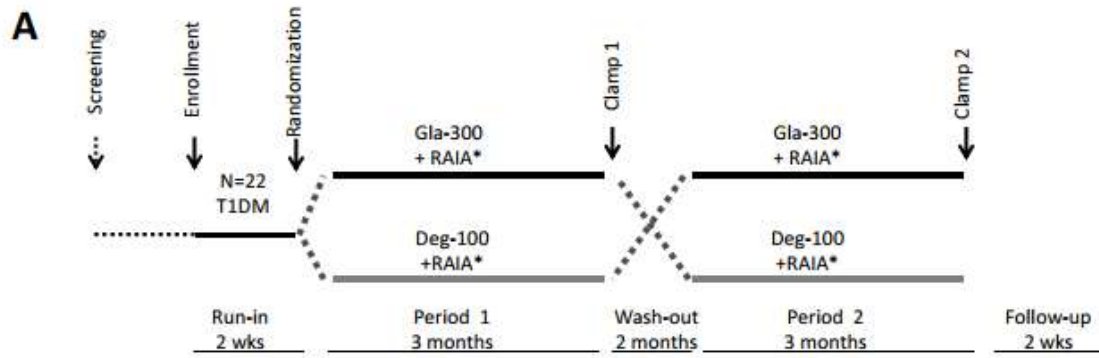
\*during the three days prior to the clamp studies.

Supplemental Table 3

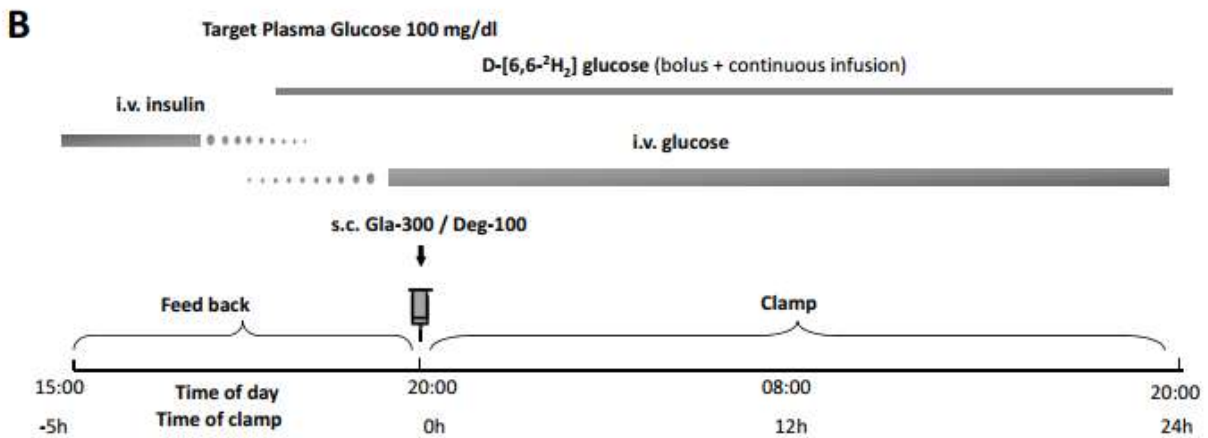
	<b>Gla-300 0.34 U/kg</b>	<b>Deg-100 0.26 U/Kg</b>	<b>Gla-300/Deg-100 ratio Point estimate<sup>a</sup> (90% CI)</b>
EGP AUC <sub>0-24 h</sub> [mg·Kg <sup>-1</sup> ]*	1001 (765; 1310)	1042 (869; 1248)	0.96 (0.81; 1.15)
EGP AUC <sub>0-12 h</sub> [mg·Kg <sup>-1</sup> ]*	549 (400; 756)	610 (514; 723)	0.91 (0.71; 1.16)
EGP AUC <sub>12-24 h</sub> [mg·Kg <sup>-1</sup> ]*	432 (325; 585)	452 (374; 547)	0.95 (0.78; 1.16)
EGP AUC <sub>0-6 h</sub> [mg·Kg <sup>-1</sup> ]*	277 (186; 414)	371 (299; 460)	0.76 (0.53; 1.10)
EGP AUC <sub>6-12 h</sub> [mg·Kg <sup>-1</sup> ]*	240 (165; 351)	218 (177; 270)	1.09 (0.85; 1.39)
EGP AUC <sub>12-18 h</sub> [mg·Kg <sup>-1</sup> ]*	233 (169; 323)	183 (126; 267)	1.27 (1.04; 1.55)
EGP AUC <sub>18-24 h</sub> [mg·Kg <sup>-1</sup> ]*	173 (126; 238)	215 (157; 295)	0.80 (0.63; 1.17)
Glucagon-AUC <sub>0-24 h</sub> [pg·h·mL <sup>-1</sup> ]*	1182 (1100; 1269)	1194 (1093; 1304)	0.99 (0.94; 1.04)
Glucagon -AUC <sub>0-12 h</sub> [pg·h·mL <sup>-1</sup> ]*	588 (549; 631)	602 (556; 651)	0.98 (0.91; 1.06)
Glucagon -AUC <sub>12-24 h</sub> [pg·h·mL <sup>-1</sup> ]*	591 (546; 641)	590 (532; 655)	1.00 (0.94; 1.05)
FFA-AUC <sub>0-24 h</sub> [mM·h·L <sup>-1</sup> ]*	7.81 (7.18; 8.50)	8.69 (8.09; 9.35)	0.90 (0.84; 0.96)
FFA-AUC <sub>0-12 h</sub> [mM·h·L <sup>-1</sup> ]*	3.26 (2.98; 5.74)	3.76 (3.37; 4.21)	0.86 (0.81; 0.94)
FFA-AUC <sub>12-24 h</sub> [mM·h·L <sup>-1</sup> ]*	4.51 (4.07; 5.01)	4.87 (4.52; 5.25)	0.92 (0.84; 1.01)
Glycerol-AUC <sub>0-24 h</sub> [mM·h·L <sup>-1</sup> ]*	1.16 (0.99; 1.37)	1.28 (1.19; 1.37)	0.91 (0.82; 1.01)
Glycerol-AUC <sub>0-12 h</sub> [mM·h·L <sup>-1</sup> ]*	0.53 (0.44; 0.63)	0.64 (0.59; 0.68)	0.86 (0.76; 0.98)
Glycerol-AUC <sub>12-24 h</sub> [mM·h·L <sup>-1</sup> ]*	0.62 (0.54; 0.72)	0.64 (0.59; 0.69)	0.97 (0.89; 1.07)
β-hydroxybutyrate-AUC <sub>0-24 h</sub> [mM·h·L <sup>-1</sup> ]*	5.31 (4.39; 6.33)	6.17 (5.41; 6.07)	0.86 (0.73; 1.01)
β-hydroxybutyrate-AUC <sub>0-12 h</sub> [mM·h·L <sup>-1</sup> ]*	2.01 (1.54; 2.61)	2.46 (2.04; 2.96)	0.82 (0.66; 0.99)
β-hydroxybutyrate-AUC <sub>12-24 h</sub> [mM·h·L <sup>-1</sup> ]*	3.15 (2.63; 3.78)	3.58 (3.04; 4.22)	0.90 (0.76; 1.06)
Alanine-AUC <sub>0-24 h</sub> [mM·h·L <sup>-1</sup> ]*	7.46 (6.96; 7.99)	7.49 (7.05; 7.96)	0.99 (0.95; 1.04)
Alanine-AUC <sub>0-12 h</sub> [mM·h·L <sup>-1</sup> ]*	3.73 (3.69; 4.13)	3.78 (3.05; 4.04)	0.98 (0.93; 1.05)
Alanine-AUC <sub>12-24 h</sub> [mM·h·L <sup>-1</sup> ]*	3.69 (3.53; 3.86)	3.68 (3.43; 3.95)	1.00 (0.96; 1.04)
Lactate-AUC <sub>0-24 h</sub> [mM·h·L <sup>-1</sup> ]*	12.2 (10.3; 13.9)	12.9 (10.3; 16.2)	0.94 (0.78; 1.13)
Lactate-AUC <sub>0-12 h</sub> [mM·h·L <sup>-1</sup> ]*	5.37 (4.44; 6.49)	6.18 (4.49; 8.51)	0.86 (0.66; 1.13)
Lactate AUC <sub>12-24 h</sub> [mM·h·L <sup>-1</sup> ]*	6.66 (5.86; 7.56)	5.97 (5.11; 6.98)	1.12 (1.02; 1.27)

\*Data are geometric mean (95% CI). <sup>a</sup> Point estimate of treatment ratios with 90% confidence interval (CIs) were calculated using a linear mixed effects model based on log-transformed data and re-transformations

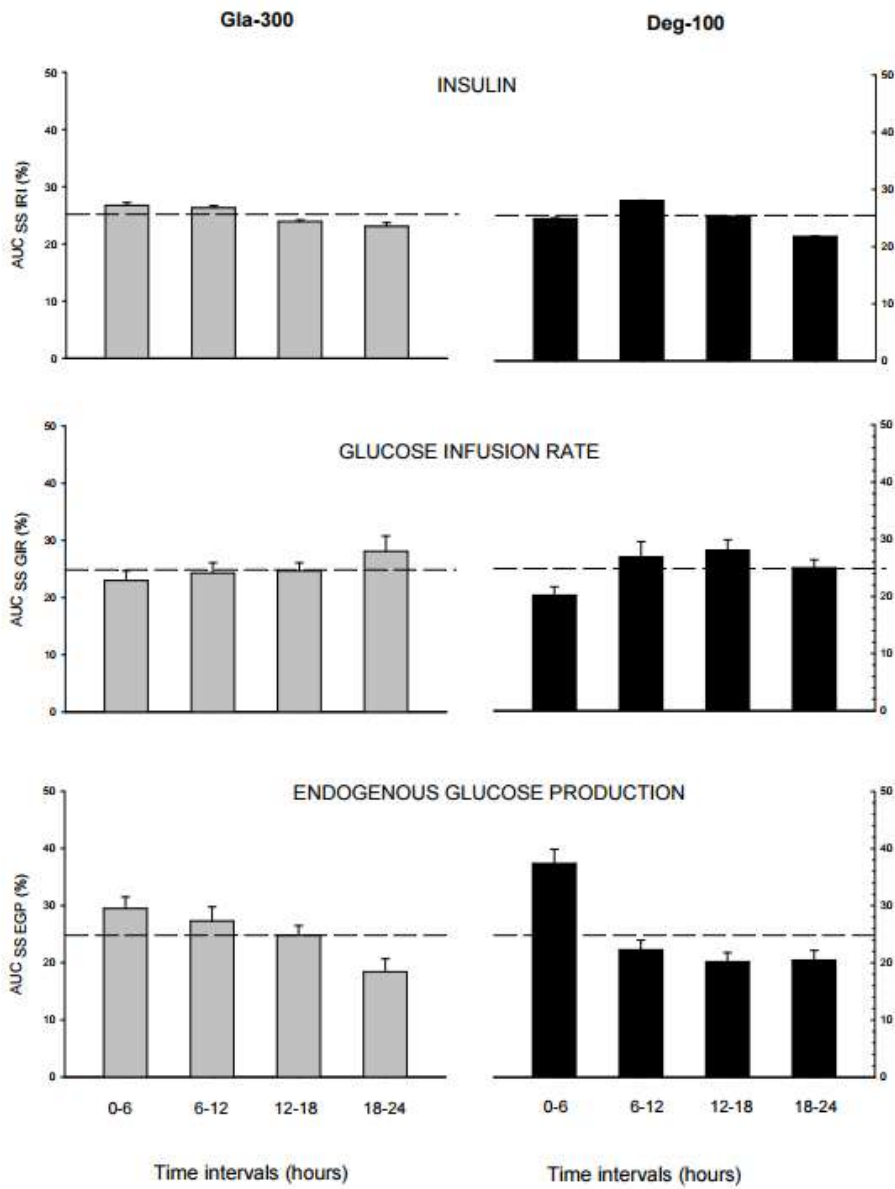
Supplemental Figure 1



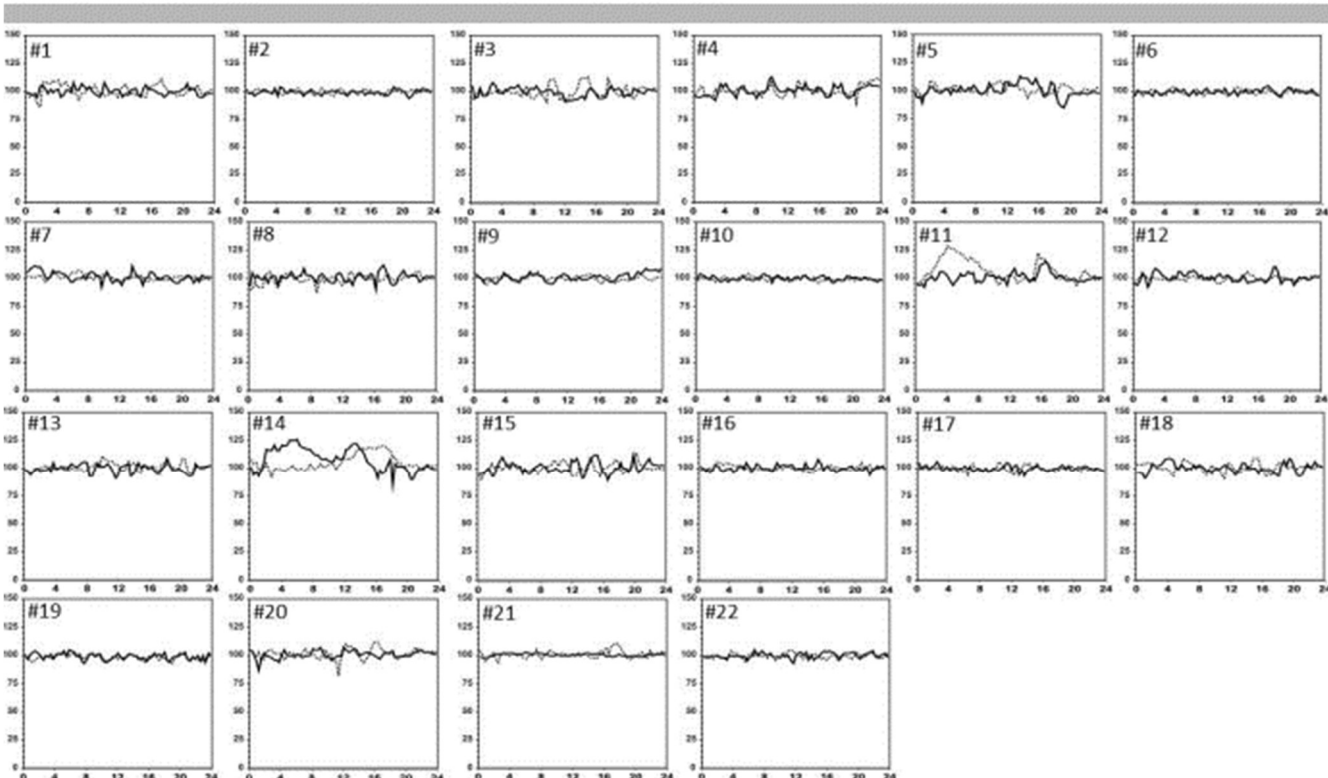
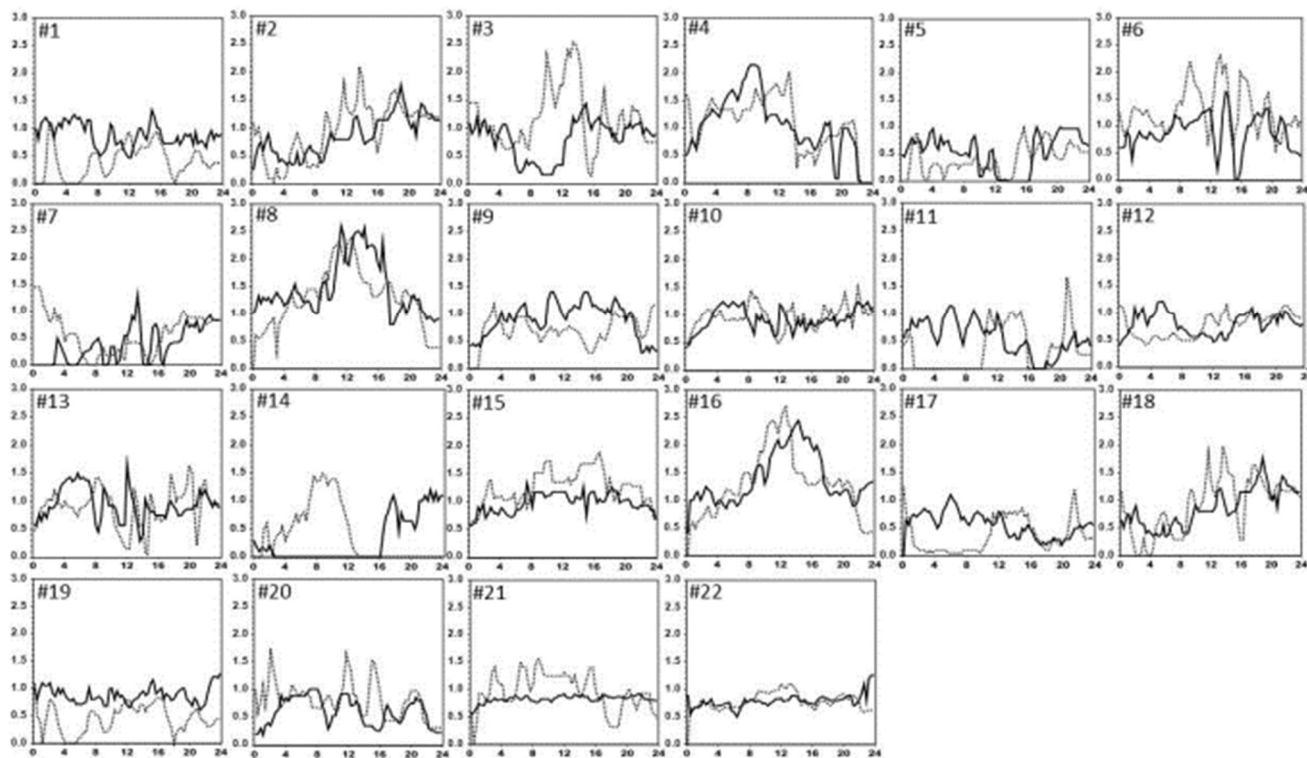
\* RAIA: rapid-acting insulin analog



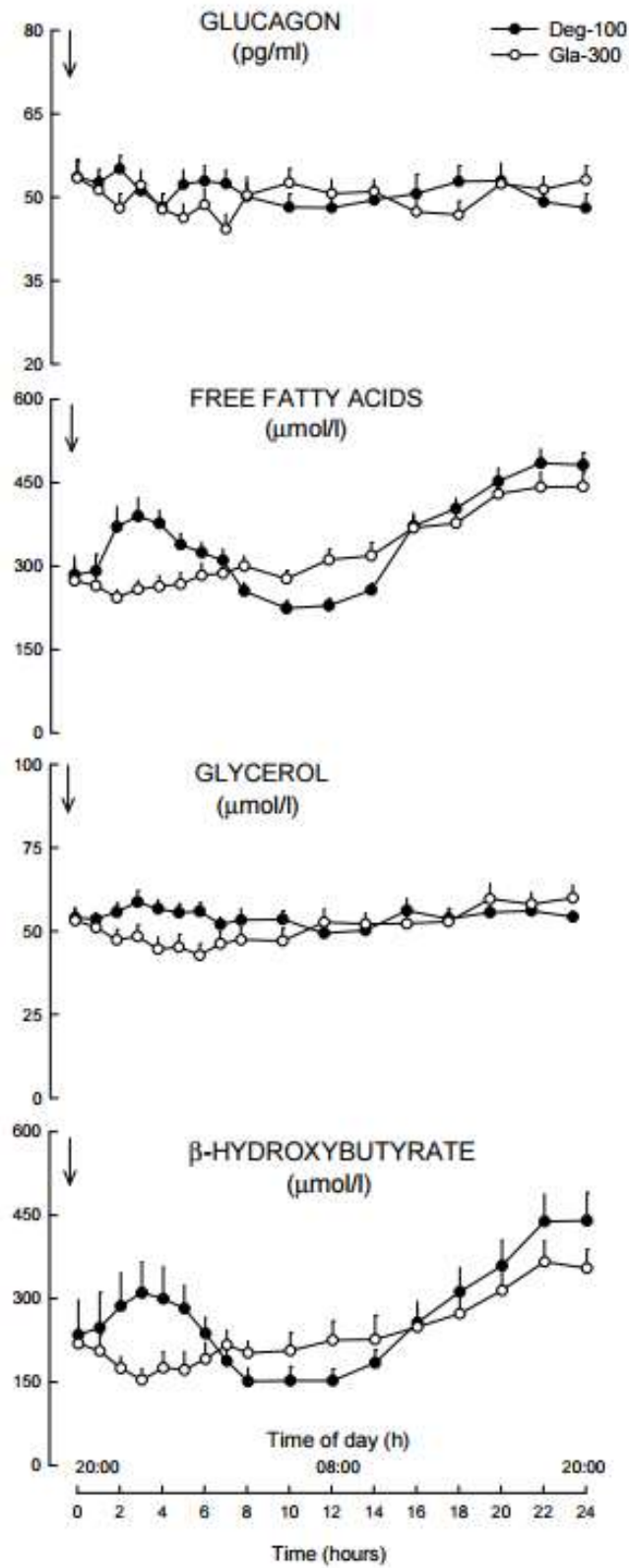
Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure S5

