Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes mellitus: a double-blind, randomized, cross-over study

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Running Title: PK and PD of glargine and detemir in T1 DM

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Received for publication 1 January 2007 and accepted in revised form 4 July 2007.

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.
Abstract

**Objective.** To compare pharmacokinetics and -dynamics (PD) of insulin glargine (GLA) and detemir (DET), 24 subjects with T1DM (38±10 years, BMI 22.4±1.6, kg/m², HbA₁c 7.2±0.7%, mean±SD) were studied after 2 week treatment with either GLA or DET once daily (randomized, double-blind, cross-over study). **Methods.** Plasma glucose (PG) was clamped at 100 mg/dl for 24-h after s.c. injection of 0.35 U/kg. Primary endpoint was end of action (time at which PG was >150 mg/dl). **Results.** With GLA, PG remained at 103±3.6 mg/dl up to 24 h (all subjects completed the study). PG increased progressively after 16 h with DET, and only 8 subjects (33%) completed the study with PG <180 mg/dl. Glucose infusion rate (GIR) was similar with DET and GLA for 12 h, after which it decreased more rapidly with DET (p<0.001). Estimated total insulin activity (GIR-AUC₀-end of GIR) was 1412±662 and 915±225 mg/Kg (GLA vs DET, p<0.05), with median time of end of action 24 h and 17.5 h (GLA and DET, p<0.001). Antilipolytic action of DET was lower than that of GLA (AUC free fatty acids₀-24 =11±1.7 vs 8±2.8 mmol/l, respectively, p<0.001). **Conclusions.** DET has effects similar to GLA during initial 12 h, but lower during 12-24 h.

Abbreviations: PK, pharmacokinetics; PD, pharmacodynamics; T1DM, type 1 diabetes Mellitus; GIR, glucose infusion rate
The soluble long-acting insulin analogs glargine and detemir exhibit more physiological pharmacokinetic (PK) and pharmacodynamic (PD) characteristics than NPH, i.e. a flatter action profile with a longer duration of action (1-3), particularly after several days of use (4), in addition to lower within subject variability (3) and lower fluctuations (5). These PK and PD advantages translate into a reduced risk of nocturnal hypoglycemia in T1DM vs NPH (6-9).

Several clinical-experimental studies have examined glargine, or detemir vs NPH, in T1 DM, but no study has compared these analogs directly, in the same subjects, at steady state, to establish the relative PK and PD of these two insulins after a therapeutic dose. However, glargine and detemir are different chemical and structural entities (1). Therefore, it is conceivable that in a head-to-head comparison, the two analogs might exhibit different PK and PD.

The aim of the present studies was to establish the PK and PD of the long-acting insulin analogs glargine and detemir in T1DM with “intra-subject” comparison at steady state, after injection of a dose of insulin similar to that used in the clinical setting in most of our T1DM patients.

RESEARCH DESIGN AND METHODS

Subjects. The study was approved by the local ethical committee and conducted according to the Helsinki declaration and GCP requirements. After giving informed, written consent, 24 T1DM subjects (14 males, 38±10 years, BMI 22.4±1.6 kg/m², HbA1c 7.2±0.7%, diabetes duration 18±7 years, fasting plasma C-peptide <0.02 nmol/l), naïve to either glargine or detemir, were recruited. All subjects had been on intensified insulin therapy with multiple daily injections of NPH as basal insulin and rapid-acting insulin analogs at meals as previously reported (10) for at least three years. Patients were free of any detectable microangiopathic complication and tested negative at the screening for autonomic neuropathy, as determined by a standard battery of cardiovascular tests (11).

Design of study. The study was a randomized, single-dose, double-blind, two-way, cross-over study, using the euglycemic glucose clamp technique (12). After a 4-week run-in period, during which the previous insulin therapy regimen was continued (10), NPH insulin was withdrawn and subjects randomized to once daily dose of either glargine (N=12 subjects) or detemir (N=12 subjects) given by syringes at 07:00 pm, for a period of two weeks. Rapid-acting insulin analogs (either lispro or aspart) were continued before each meal. The dose of basal insulin was titrated to reach fasting plasma glucose of 100 mg/dl, while avoiding nocturnal hypoglycemia (plasma glucose <72 mg/dl) (10). The dose of rapid-acting analog was titrated to keep the 2-h post-prandial plasma glucose <145 mg/dl, but >72 mg/dl. For the entire duration of studies, all subjects monitored blood glucose by means of a reflectometer (One Touch Ultra, Lifescan, Johnson & Johnson, Milpitas, CA).

After 14-day treatment all subjects underwent an euglycemic clamp for 24 hours, following s.c. injection of the basal insulin they were on, either glargine (0.35 U/kg) or detemir (0.35 U/kg) (2). This was followed by a wash-out period of two weeks, during which they resumed the insulin regimen of the run-in period. The subjects were then crossed-over to the other basal insulin, and at the end of the last two weeks, were studied again with the euglycemic clamp technique for 24 hours.

Euglycemic clamp. The procedure previously described for the euglycemic clamp (2) was used, but the target plasma glucose was 100 mg/dl and time “0 min” of study was 07:00 pm (s.c. injection of the basal insulin analog). The last s.c. injection of rapid-acting insulin analog was at 12:00 noon (before a standardized meal: 688 kcal, 54% carbohydrate, 30% protein,
and 16% lipids), and an i.v. feed-back insulin infusion was initiated at 02:30 pm to maintain plasma glucose 118-135 mg/dl between 03:00-05:00 pm and at 100 mg/dl until 07:00 pm (2). The study was terminated at 24 hours after the s.c. injection of glargine or detemir, or earlier if plasma glucose increased to above 180 mg/dl in the absence of glucose infusion. To ensure blinding, a simple randomization was used based on computer-generated random numbers by a person who was not involved in establishing eligibility and entry of patients. Concealment of the randomization was ensured by having the allocation codes in a locked unreadable computer file handled by a designated investigator, who assigned subjects insulin cartridges corresponding to the 2 weeks of treatment (13). The same independent investigator gave subjects the s.c. injection of glargine or detemir insulin in all clamp studies, by means of an insulin syringe (abdominal area).

Analytical methods. Bedside plasma glucose was measured in triplicate using a Beckman Glucose Analyzer (Beckman Instruments, Palo Alto, CA, USA). Plasma C-peptide was measured by RIA (Linco Research, St. Charles, MO, USA). Plasma insulin was measured using a two-site sandwich chemiluminescent immunoassay for human insulin (MLT Ltd, Cardiff, UK). The validation process with insulin glargine indicated that cross-reactivity is approximately 100% that of human insulin, whereas with insulin detemir the cross-reactivity is 200-300% that of human insulin. In all studies, plasma insulin was measured after extraction of antibodies with 30% polyethylene glycol (14). With this assay, greater values of insulin are expected with detemir vs glargine. In fact, insulin detemir is formulated with a greater molar ratio than human NPH and glargine (4:1:1, respectively), and, in addition, the assay does not distinguish between free and albumin-bound detemir, the latter accounting for 98-99% of circulating levels (15). HbA1c was determined by high performance liquid chromatography using an HI-Auto A1c TM HA 8121 apparatus (DIC, Daaichi, Kogaku Co., Ltd., Kyoto, Japan) (DCCT aligned non-diabetic subjects <6.1%).—Plasma glycerol, β-hydroxybutyrate, lactate, and alanine were measured by previously described fluorometric assays (16). Plasma free fatty acid (FFA) concentrations were measured using a commercial kit (Wako NEFA C test kit; Wako Chemicals, Neuss, Germany).

Calculations. Pharmacodynamic parameters of insulin action were calculated as follows: a) onset of insulin action: time at which i.v. glucose was initiated after s.c. insulin injection; b) minimal duration of action: time at which plasma glucose increased >118 mg/dl; c) end of action: time at which plasma glucose was consistently (for at least 30 minutes) >150 mg/dl; and d) end of study: time at which plasma glucose was consistently >180 mg/dl.

Insulin activity profile. Three variables account for insulin action during pharmacodynamic clamp studies: a) the rate of i.v. insulin infusion (IIR), which may be needed in the initial part of the clamp study to compensate for the lag in onset of action of s.c. injected insulin with retarded activity; b) plasma glucose concentration (PG); and c) the rate of glucose infusion (GIR) required to maintain the target PG. Ideal basal insulin should maintain the target PG in the absence of GIR and/or IIR. We have modified the insulin activity profile formula by Radziuk et al. (17) that allows interpretation of simultaneous changes of PG, GIR, and IIR following s.c. insulin injection, without determination of endogenous glucose production:

\[
\frac{[(\text{Target PG} / \text{Actual PG}) \%] + [(\text{Actual GIR} / \text{Total GIR}) \%] – [(\text{Actual IIR} / \text{Baseline IIR}) \%]}{2}
\]

Statistical analysis. The linear trapezoidal rule was used to calculate the area under curve (AUC) for plasma insulin, plasma glucose, glucose infusion rates and non-glucose substrates. Maximum plasma concentration (Cmax) and the time to reach
C\textsubscript{max} (T\textsubscript{max}) for the same variables were read directly from the plasma concentration-time data for each subject. GIR data were smoothed by taking a three point moving average in order to provide reliable data for calculation of GIR C\textsubscript{max} and GIR T\textsubscript{max}. The primary analysis of the PK/PD parameters was performed on log-transformed data using analysis of variance (ANOVA) which allowed for variation due to sequence, subjects nested within sequence, period, and treatment. The mean differences between treatments were estimated along with their 95% confidence intervals (CI). The ratio between antilogged treatment means and the corresponding antilogged CIs were calculated. T\textsubscript{max} variables, onset of action, duration of action and end of action were analyzed non-parametrically. The Wilcoxon rank-sum test was used to perform crossover analyses and Hodges-Lehmann estimates of the treatment effect were computed with 95% CIs (18, 19). No significant treatment carry-over effects were found for any of the data presented. Regression analysis on insulin concentrations after transformation to z-scores was done by using the least square method. The primary endpoint of the study was time to end of action. With a sample size of 24 subjects the two-sided test at the 5% significance level of a 2x2 cross-over design had 80% power of detecting a difference of duration of action of 5 h between the treatments with the SD of the differences of 4 h.

RESULTS
All of 24 subjects enrolled completed the two euglycemic clamp studies.

Glycemic control and insulin doses
Glycemic control (mean blood glucose from home monitoring data over days 1-14) was not different with glargine 131±12 mg/dl and detemir 134±9 mg/dl (p=0.417).

Total daily insulin dose (U/kg, values over 3 days prior to studies) during treatment with detemir (0.70±0.07) was higher than with glargine (0.65±0.06) (p=0.001), due to a greater dose of rapid-acting analog with detemir (0.38±0.05) vs glargine (0.33±0.05, p=0.001), primarily because of need for more frequent correction boluses in the afternoon (0.03±0.02 vs 0.01±0.02, p=0.007). The dose of glargine (0.33±0.02) was essentially the same as that of detemir (0.32±0.03) (p=0.095).

Plasma glucose levels immediately before lunch were 137±24 mg/dl and 133±27 mg/dl for glargine and detemir, respectively (p=0.638), and doses of rapid-acting analog before lunch were not different between treatments (0.12±0.02 vs 0.13±0.03 U/Kg, glargine vs detemir, p=0.263). Similarly, plasma glucose prior to i.v. insulin infusion (2:30 pm) was no different in the two treatments (glargine 149±49 mg/dl and detemir 145±40 mg/dl, p=0.306).

Rates of i.v. insulin and glucose infusion, plasma glucose concentration, insulin activity profile, and number of subjects in study (Figure 1, Table 1)

The amount of regular insulin infused i.v. from -4.5 to 0h (pre-injection period) to maintain euglycemia was nearly twice as high with detemir (4.0±1.7 U) vs glargine treatment (2±1 U) (p<0.001). After the s.c. injection of basal insulin at time 0h (7:00 pm), the rate of i.v. insulin infusion remained greater with detemir (0.29±0.40 mU·Kg\textsuperscript{-1}·min\textsuperscript{-1}) vs glargine (0.11±0.19 mU·Kg\textsuperscript{-1}·min\textsuperscript{-1}, p=0.038). The median time of i.v. insulin withdrawal was longer with detemir (60 min, 95%CI: 0; 90) vs glargine (30 min, 95%CI: 0; 60), but the difference was not statistically significant (p=0.145).
The plasma glucose concentration at time-point 0 with detemir and glargine were similar (99.0±5.5 mg/dl and 100.0±3.5 mg/dl, respectively, p= 0.142). During the first twelve hours of the study, the two treatment groups had similar mean values AUC0-12h corresponding to mean plasma glucose concentrations of 100.0±1.9 mg/dl and 101.0±2.9 mg/dl with detemir and glargine, respectively (p= 0.111). Similarly, the between-subjects variability of plasma glucose was low in both treatment groups (c.v. values <3.0%). In the second half of the study period (time 12-24h), the mean plasma glucose concentrations was higher with insulin detemir 137±17 mg/dl than glargine 104±4 mg/dl, (AUC12-end of study: 1430±221 vs 1248±45 mg/dl, respectively, p=0.002). Although onset of action was no different between the two insulins, the minimal duration of insulin action was shorter, with an end of insulin action and end of study time earlier with insulin detemir as compared to glargine (Table 1). By the end of the clamp study (time 24h), the duration of insulin action can not be estimated beyond this time point for those subjects whose plasma glucose levels remained <150 mg/dl at 24h (underestimation).

Pharmacodynamic variables calculated from the glucose infusion rate (GIR) of Figure 1 are contained in Table 1. The mean GIR for the 24 h study period (AUC0-end of GIR) was greater with glargine than detemir. However, over the initial 12 h period (AUC0-12h), the GIR with glargine and detemir were equivalent. The mean GIR for the second 12 h period (AUC12-end of GIR) was lower by ~80% with detemir as compared to glargine. Although GIR Cmax was similar with the two basal insulin analogs with no distinct peak, maximum insulin activity (GIR T_max) was reached at median time of 7 h after treatment with detemir and 4 h after treatment with glargine.

The insulin activity profiles, as derived from the above described formula (see methods), indicated an earlier and greater activity throughout the study with insulin glargine (108±30 %) compared to detemir (60±29 %) (p<0.01).

Plasma insulin and substrate concentrations (Figure 2, see on-line appendix)

As expected, the overall plasma insulin concentrations were higher with detemir than with glargine (Figure 2, on line appendix [available at http://care.diabetesjournals.org]). Within-treatment comparisons indicated that insulin levels (AUC) were higher during the first 12-h period than the second 12-h period of the study, both with detemir (4572±1478 vs 2209±1105 µU/ml, p<0.001) and with glargine (420±202 vs 332±138 µU/ml, p<0.001). However, the rate of plasma insulin disappearance, was five times greater for insulin detemir as compared to glargine (z-scores -2.40±0.15 vs -0.50±0.05, respectively, p<0.001).

Plasma concentrations of substrates indicating primarily lipolysis (FFA and glycerol) and ketogenesis (β-hydroxybutyrate) were higher with detemir as compared to glargine from 12-h to the end of study. In fact, FFA, glycerol and β-hydroxybutyrate were, respectively, 29% (95% CI: 11; 44) (p=0.004), 22% (95%CI: 4; 37) (P=0.023) and 52% (95%CI: 28; 68) (p=0.001) greater with detemir. In addition, FFA were greater with detemir also during the initial 12 h [33% (95% CI: 15; 47) (p=0.002)]. Lactate concentrations were not different between treatments. Overall alanine levels decreased with both treatments although they were 9% (95% CI: 3; 14) (p=0.007) higher with detemir as compared to glargine.
PK and PD of glargine and detemir in T1 DM

DISCUSSION

The present report describes the PK/PD of insulin detemir and glargine at steady state in subjects with T1DM in response to a dose reproducing closely that used during the two weeks prior to studies to optimize post-absorptive plasma glucose.

The end of action was earlier with detemir than with glargine, whereas the onset of action was no different (Table 1). As far as the former is concerned, since the study terminated at 24h, end of action is underestimated in those subjects (13% with detemir and 100% with glargine) whose plasma glucose remained < 150 mg/dl by 24 h.

In the present study we propose “minimal end of action” as meaningful PD parameter for estimating activity of basal insulin. An ideal basal insulin should restrain endogenous glucose production to keep fasting plasma glucose <100 mg/dl. A criterion of “minimal duration of action” (time at which plasma glucose >118 mg/dl) may help more than “end of action” (plasma glucose >150 mg/dl) in understanding the appropriateness of the replacement of basal insulin in subjects with DM treated to target (21).

With regard to the definition of the onset of action and the target plasma glucose of the clamp, the present study is different from previous studies (2, 22). In fact, because of the ongoing activity of basal insulin injected the day(s) before, the definition of the onset of action has been based on the time of initiation of GIR rather than on the change in rate of i.v. insulin. In addition the target plasma glucose of the clamp has been lowered from 130 mg/dl to 100 mg/dl, the latter being the currently accepted goal of fasting in intensive insulin treatment.

One of the most important metabolic actions of insulin is to prevent lipolysis (23). In the present study, the duration of the anti-lipolytic action of the s.c. injected long-acting insulin analogs differ, with plasma FFA increasing earlier with detemir than with glargine even during the initial 12h of study where activity of detemir and glargine on glucose metabolism were equivalent. Similarly, plasma β-hydroxybutyrate increased over 3.0 mmol/l by end of study with detemir, but only to ~1.5 mmol/l with glargine. Overall, the anti-lipolytic activity of detemir was lower than that of glargine (Fig. 2, on-line appendix). This reflects the in vitro data where detemir is estimated to possess only ~27% lipogenic potency vs human insulin (24).

To the best of our knowledge, this is the first study comparing potency of detemir and glargine in subjects with T1DM. In the present study, 1 U of detemir (24 nmol insulin) was ~30% less active than 1 U of glargine (6 nmol insulin) in terms of total glucose infused. This would explain at least in part, the shorter end of action and lower anti-lipolytic effect of detemir. If confirmed, these results would indicate that in T1DM detemir reaches bioequivalence to glargine at a molar ratio greater than the presently formulated 4:1 vs human insulin. Interestingly, in normal, non-diabetic subjects equipotency has been reported with a molar ratio detemir:NPH of 5:1 (25).

Traditionally, in clamp studies insulin action has been derived by the rate of glucose infusion (2-4). However, GIR does not totally reflect insulin action either in the early, or in the late part of the clamp. In the early part, i.v. insulin infusion is the (negative) indicator of s.c. injected insulin.

Later, when GIR decreases and becomes zero, it is the rate of increase in plasma glucose which indicates (negatively) the action of s.c. injected insulin. The activity profile formula (see methods) allows estimate of onset of insulin action better than those derived solely from the GIR. The activity profiles of detemir and glargine exhibit a similar plateau between 2-13 hours,
PK and PD of glargine and detemir in T1DM after which glargine remains at steady activity close to 100% until the end of the 24 h study period, whereas detemir showed a progressive decrease in activity was observed after 12 h, reading 55% at 24 hours. In the present study, subjects without endogenous insulin secretion (T1DM) have been studied to specifically assess the effect of the PK/PD profile of the s.c. injected “basal” insulin analogs glargine and detemir. The presence of endogenous insulin secretion, either normal (non-diabetic subjects) or impaired (T2DM), contributes, to some extent, to the action of insulin injected s.c., therefore the interpretation of such results is limited. Also, because of the large inter-individual differences in PK and PD (3), it is more important to conduct cross-over, not parallel group, studies (3, 27). These considerations are likely to account for the different findings of PK and PD in the present study as compared to previous studies in T2DM (28), especially with parallel groups (27).

In one study in T1DM (3), with insulin dose greater than in the present study (0.4 vs 0.35 U/kg), both glargine and detemir exhibited identical median end of action (24h, personal communication, courtesy of T. Heise), whereas it was 4.5h (median time) longer for glargine in the present study (Table I). However, it is difficult to compare the results of Heise et al. (3) with those of the present study because of the different study design, and use of biostator. In the study by Plank et al. (22) replicating the clamp method of our previous study (2), a full dose-response of progressively increasing dose of detemir from 0.1 up to 1.6 U/kg was elegantly described. In that study (22), however, insulin doses lower than 0.4 U/Kg (0.1 and 0.2 U/Kg) showed that the end of action data were asymmetrically distributed with positive skeweness (mean values greater than medians, personal communication, courtesy of T. Pieber) as they are in our study using 0.35 U/Kg. In fact, in our study, the mean and standard deviation values of the end of action for insulin detemir were 19.4h and 2.9h, respectively, and the median 17.5h. Conversely, in the study by Plank et al. 0.4U/Kg (or higher doses) of detemir resulted in longer end of action in the majority of subjects studied as indicated by greater median values (22.7h) than mean values (21.5±3.3h). Therefore, in addition to the different population studied, the simplest explanation to reconcile the longer (Plank et al. [22]) with the shorter median of present study (Table I), is the higher detemir dose used by Plank et al. (22). Also, methodological differences between the Plank et al. study (22) and the present study, might have affected calculation of end of action, such as the different PG target (130 vs 100 mg/dl, respectively) and the steady state condition (present study) vs first dose (22). The latter difference is important when long-acting insulin analogs are studied, since also with glargine the end of action is different after first dose vs 1 week of use (4). However, the aim of the present study was not to re-establish the end of action of detemir, or glargine isolatedly, in “absolute” terms. Rather it was to compare PK and PD of the two basal insulins “relatively” to each other, when tested at the doses used by the subjects with T1DM in study to optimize every day post-absorptive plasma glucose.

The PK/PD findings of the present study indicate that glargine should be once-daily basal insulin in subjects with T1DM, whereas detemir appears to be twice-daily basal insulin in the majority of subjects. However, the question of clinical use of detemir is open to debate. A clinical trial has reported non-inferiority with detemir once- as compared to twice-daily in T1DM in terms of percentage of A1C (29). In an observational trial, 49% of subjects with T1DM were treated with detemir once daily (30). On the other hand, several trials designed to optimize replacement of basal insulin needs with detemir, have used detemir twice daily in T1DM (26, 31). In the small group of subjects of the present study followed for two weeks, detemir was successfully used
once daily, but the dose of rapid-acting insulin at lunch was increased more, and a correction bolus in mid-afternoon was given more frequently as compared to glargine. Additional studies exploring optimized regimens of detemir insulin in T1DM, are needed.

ACKNOWLEDGMENTS
This study is dedicated to the persons with T1DM who have volunteered the study. The study was an independent, investigator-designed project, neither shared with, nor supported by, any pharmaceutical company.

CONFLICT OF INTEREST
G.B. Bolli has received honoraria for scientific advising and consulting from the following companies: Sanofi-aventis, NovoNordisk, Eli-Lilly & Co.
References


Table 1  Onset of action and duration of action of insulin detemir and insulin glargine, and pharmacodynamic variables after subcutaneous injection of insulin detemir and insulin glargine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Detemir</th>
<th>Glargine</th>
<th>point estimate (%)</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action [h] (^b) ((time at which GIR was started))</td>
<td>1.3 (1;2)</td>
<td>1.3 (1;3)</td>
<td>0</td>
<td>-0.25 ; 0.25</td>
<td>0.818(^c)</td>
</tr>
<tr>
<td>Minimal duration of action [h] (^b) ((time at which PG&gt;6.5 mmol/l))</td>
<td>15.5 (13;24)</td>
<td>24 (22;24)</td>
<td>-7.75</td>
<td>-8.5 ; -6.75</td>
<td>0.000(^c)</td>
</tr>
<tr>
<td>End of action [h] (^b) ((time at which PG&gt;8.3 mmol/l))</td>
<td>17.5 (16;24)</td>
<td>24 (23;24)</td>
<td>-4.5</td>
<td>-6.2 ; -3.25</td>
<td>0.000(^c)</td>
</tr>
<tr>
<td>End of study [h] (^b) ((time at which PG&gt;10 mmol/l))</td>
<td>21.5 (17;24)</td>
<td>24 (24;24)</td>
<td>-2.25</td>
<td>-3.3 ; -1.5</td>
<td>0.001(^c)</td>
</tr>
<tr>
<td>AUC GIR(_{0-24,h}) [mg/kg]</td>
<td>915±225</td>
<td>1412±662</td>
<td>70.3</td>
<td>53.4 ; 92.7</td>
<td>0.015</td>
</tr>
<tr>
<td>AUC GIR(_{0-12,h}) [mg/kg]</td>
<td>773±200</td>
<td>807±352</td>
<td>97.7</td>
<td>78.5 ; 121.6</td>
<td>0.832</td>
</tr>
<tr>
<td>AUC GIR(_{12-end, of, infusion}) [mg/kg]</td>
<td>142±194</td>
<td>605±390</td>
<td>17.4</td>
<td>8.2 ; 36.7</td>
<td>0.000</td>
</tr>
<tr>
<td>GIR C(_{max}) [mg·kg(^{-1})·min(^{-1})]</td>
<td>1.6±0.5</td>
<td>1.8±0.6</td>
<td>90</td>
<td>78.0 ; 103.7</td>
<td>0.137</td>
</tr>
<tr>
<td>GIR T(_{max}) [h](^b),(^c)</td>
<td>7 (2; 12)</td>
<td>4 (1; 24)</td>
<td>3.25</td>
<td>0.5 ; 5.3</td>
<td>0.035(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Point estimates for treatment effect are based on the Hodges-Lehmann estimate of the median difference with the associated 95% CI (Onset, minimal duration, end of action, end of study and GIR T\(_{max}\)). Point estimates and 95% confidence intervals for the ratio of
treatment means are based on adjusted means derived from ANOVA (AUC GIR$_{0-24\,h}$, AUC GIR$_{0-12\,h}$, AUC GIR$_{12\,\text{end of infusion}}$ and GIR $C_{\text{max}}$).

$^b$ Median (min;max).

$^c$ $p$-value from the Wilcoxon rank sum test.
Legends to Figures

Figure 1  Rates of i.v. insulin infusion, plasma glucose, rates of i.v. glucose infusion, insulin activity profile, and numer of subjects in the study (plasma glucose <180 mg/dl, 10 mmol/l) after s.c. injection of insulin detemir or insulin glargine