Clinical safety of insulin detemir in patients with Type 2 diabetes in the Gulf countries: The multicenter, noninterventional, open-label LevSafe study

Abdel Rahman El Shiekh, Hesham A. Farrag1, Tarek Ashour2, Khalid Zaki Alshali3, Waleed AbdelFattah4

Department of Internal Medicine and Endocrinology, King Abdulaziz University, Jeddah, Chairman of Saudi Scientific Diabetes Society, 1Department of Internal Medicine, Saudi Airlines Medical Services, Jeddah, 2Department of Internal Medicine, Security Forces Hospital, Riyadh, 3Department of Medicine, King Abdulaziz University, Jeddah, 4Clinical, Medical, and Quality Department, Novo Nordisk Pharma Gulf, Riyadh, Saudi Arabia

A B S T R A C T

Aim: To evaluate the safety profile of insulin detemir (IDet) in people with Type 2 diabetes mellitus (T2DM) in the Gulf countries in the 32-week, noninterventional LevSafe study. Methods: People with T2DM whose physicians had opted to start IDet therapy were included in the study. Safety parameters, including serious adverse drug reactions (SADRs) and hypoglycemia, and changes in body weight and glycemic control were evaluated at baseline, week 16 and week 32. Results: A total of 686 patients were exposed to IDet therapy with a mean (±standard deviation) age, body mass index, and diabetes duration of 51.3 ± 11.0 years, 31.3 ± 5.5 kg/m², and 10.2 ± 6.1 years, respectively. The mean total daily dose of IDet was 32.0 ± 32.8 U at baseline and 44.7 ± 60.7 U at week 32. No SADRs were reported during the study. Total hypoglycemia decreased from 435 events at baseline to 204 events at week 32 (mean change analyzed by Wilcoxon signed rank test: −0.34; P = 0.0115), and no major hypoglycemia was reported at week 32. Over the 32-week treatment period, the mean body weight decreased from 85.7 ± 15.2 kg to 85.4 ± 14.5 kg (P = 0.0203), glycated hemoglobin A1c from 9.9 ± 1.67% to 7.7 ± 1.36% (P < 0.0001), and fasting plasma glucose from 11.9 ± 3.27 mmol/L to 7.4 ± 1.85 mmol/L (P < 0.0001). Conclusion: IDet therapy was well-tolerated and was associated with a decreased number of hypoglycemic events and improved glycemic control after 32 weeks in patients with T2DM in the Gulf countries.

Key words: Gulf, insulin detemir, LevSafe, noninterventional study, Type 2 diabetes

INTRODUCTION

Rapid urbanization, the adoption of high-energy diets, and limited physical activity have resulted in a marked increase in Type 2 diabetes mellitus (T2DM) prevalence in the Middle East.[1] Three Gulf countries, Kuwait, Qatar, and Saudi Arabia, are currently among the top 10 worldwide in terms of T2DM prevalence.[2]

Alarmingly, a 2011 study by Alhyas et al. revealed that many patients with T2DM in the Gulf region continue to experience high levels of blood glucose in clinical practice.[3] This finding suggests that suitable therapeutic intensification in line with the internationally
prescribed guidelines for the management of T2DM such as the joint guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation guidelines for Type 2 diabetes is not followed consistently in clinical practice.\[^{4,5}\]

Weight gain and the fear of hypoglycemia are acknowledged as key limiting factors to the timely initiation and intensification of traditional insulin therapy.\[^{6}\] Basal insulin analogs have been developed to address the problems associated with attaining a near-normal physiologic insulin profile using traditional insulin therapy.\[^{7}\]

Treatment with insulin detemir (IDet), a long-acting basal insulin analog, results in lower within-subject variability in fasting plasma glucose (FPG) levels compared to neutral protamine Hagedorn (NPH) insulin.\[^{8}\] Unlike other basal insulins such as NPH insulin and insulin glargine that are associated with greater fluctuations in absorption kinetics, IDet has a more physiologic action profile and is consequently associated with a lower risk of hypoglycemia, particularly in the nocturnal period.\[^{9}\] IDet therapy is associated with a low incidence of hypoglycemic events in randomized clinical trials and observational studies.\[^{10-13}\] Clinical studies have also shown that IDet therapy results in less body weight gain compared to NPH insulin and insulin glargine.\[^{14,16}\]

Although the safety of IDet has been examined in several randomized controlled trials,\[^{10,11,14-16}\] safety data from the Gulf region in a real world setting are limited. It would be valuable to study a heterogeneous population of patients with T2DM to establish if any subsets are at increased risk of severe hypoglycemia through an observational study using actual clinical practice settings. It is recognized that data from observational studies can provide a more comprehensive safety profile of a drug when compared to randomized controlled trials due to the inclusion of more representative patient populations.\[^{17}\] Randomized controlled trials typically exclude patients who are at risk of recurrent severe hypoglycemia; hence, observational studies with less restrictive selection criteria could provide important information on the clinical experience of such patients in actual practice.\[^{18}\] Furthermore, such a study would permit evaluation not only of the safety profile of IDet but also of diverse physician choices in T2DM management. Therefore, the LevSafe study was conducted in the Gulf countries with the aim of evaluating the safety of IDet in patients with T2DM under normal clinical practice conditions.

### METHODS

#### Study design and settings

LevSafe was a noninterventional, nonrandomized, multicenter, open-label, prospective, and postauthorization study in the Gulf countries. This was a 32-week study conducted to evaluate the safety of IDet (Levemir\(^{\text{®}}\), Novo Nordisk A/S, Bagsvaerd, Denmark) under normal clinical practice conditions in patients with T2DM. Patients were recruited between May 19, 2008, and October 31, 2009, across 33 centers (both primary and secondary care physicians who prescribed insulin) in Kuwait, Oman, Saudi Arabia, and the United Arab Emirates.

IDet was prescribed by the physician as the result of a normal clinical evaluation. As this was a noninterventional study, there was no comparator treatment. IDet was commercially available and administered by subcutaneous injection.

The physician determined the starting dose and frequency of administration, as well as later changes to either dose or frequency, if any. Concomitant use of oral glucose-lowering drugs (OGLDs) and other insulins was permitted at the discretion of the physician. Any adjustments to the timing and dose of IDet therapy, including any change to concomitant insulin or OGLDs were at the discretion of the physician.

There were no study-prescribed procedures for this noninterventional study. Any procedure ordered by the physician during this study was one that was appropriate to the routine care delivered to the patient at the discretion of the participating physician.

#### Patients

After the physician decided to use IDet therapy, any patient with T2DM was eligible for the study, including newly diagnosed patients who had never received insulin or insulin analogs previously. The selection of the patients was at the discretion of the individual physician.

Patients who were considered unlikely to comply with the study protocol were excluded, as were patients already receiving IDet or with a hypersensitivity to IDet or any of its excipients. Children below the age of 6 years, pregnant women, and women who were breastfeeding or had the intention of becoming pregnant within the next 8 months were also excluded.

The LevSafe study was approved by the Ethics Committees and other regulatory authorities, as applicable, of each
participating country. All patients provided oral informed consent prior to their participation in the study as written informed consent was not mandatory according to local regulations in the participating Gulf countries at the time this study was conducted.

Study visits and measurements
The physicians evaluated the patients at routinely scheduled clinic visits comprising a baseline visit (week 0), an interim visit (week 16), and the final visit (week 32). At each visit, the physician gathered information from the patient's recall, the patient's notes, and the patient's self-monitoring blood glucose diary. All data were recorded using a standard case report form.

At baseline, the data collected by the physician comprised the patient's eligibility, demographic data, medical history (including the number of total and major hypoglycemic events [daytime vs. nocturnal]) experienced over the past 4 weeks from the patient's recall, the most recent glycated hemoglobin A1c (HbA1c) value, the most recent FPG value over the previous 4 weeks, pregnancy status using the human chorionic gonadotropin test for female patients and the physician's orders with the reason for starting IDet therapy, dose, and timing of administration.

A hypoglycemic event was defined as an event with one of the following characteristics: (1) Symptoms of hypoglycemia that resolved with oral carbohydrate intake, glucagon, or intravenous glucose, (2) any symptomatic or asymptomatic blood glucose <50 mg/dL (2.8 mmol/L).

A nocturnal hypoglycemic event was defined as an individualized symptomatic event consistent with hypoglycemia that occurred while the patient was asleep between bedtime after the evening insulin injection and before getting up in the morning (before morning determination of FPG and morning injection).

A major hypoglycemic event was defined as an event with severe central nervous system symptoms consistent with hypoglycemia in which the patient was unable to treat himself/herself and had one of the following characteristics: (1) Blood glucose <50 mg/dL (2.8 mmol/L), or (2) reversal of symptoms after either food intake or glucagon or intravenous glucose administration.

At the interim and final visits, the physician recorded the patient's body weight and medical history (including the timing and dose of IDet therapy and other concomitant glucose-lowering therapies, the number of total and major hypoglycemic events experienced over the past 4 weeks using the same definitions from the baseline visit, and the most recent values of HbA1c and FPG).

Outcomes and assessments
The primary endpoint was the incidence of serious adverse drug reactions (SADRs), including major hypoglycemic events, during 32 weeks of IDet therapy.

The secondary safety endpoints were the number of serious adverse events (SAEs); the number of all adverse events (AEs); and the number of all, daytime, and nocturnal hypoglycemic events at baseline compared to week 32.

The effectiveness parameters assessed during the study were the change in body weight and HbA1c from baseline to week 32 and fasting glucose control as measured by FPG after approximately 16 and 32 weeks of treatment compared to baseline.

Statistical methods
The sample size calculation was based on the primary objective to evaluate the incidence of SADRs. A sample size of 500 patients would provide a probability of 95% of detecting SADRs with an incidence of at least 0.75%, assuming a dropout rate of 20%, i.e., 500 patients would provide a 95% certainty of detecting at least one SADR that occurs with an incidence of 75 in 10,000 after taking into account a dropout rate of 20%.

The full analysis set (FAS) consisted of all patients enrolled in the study and initiated IDet therapy. The efficacy analysis set (EAS) included all patients from FAS, who had a final visit and at least one measurement concerning HbA1c, FPG, and body weight at baseline and final visit. The analysis of all variables, including safety and efficacy outcomes, was performed for the FAS and the analysis of efficacy outcome variables was performed for the EAS. For withdrawn patients, valid data up to the date of withdrawal were included in the analysis.

All statistical analyses were performed by Novo Nordisk using SAS®, Version 9.1. Continuous variables were summarized using summary statistics (mean and standard deviation [SD]) while discrete ordinal variables and categorical variables were summarized using frequencies and percentages (n [%]). Missing observations were not replaced.

The proportion of patients reporting hypoglycemic events and the number of events/patient-year at baseline and week 32 was presented stratified by type (overall or major events) and time of occurrence (daytime or nocturnal events).

The significance level for two-sided statistical testing was set at 5%. The mean changes in body weight, HbA1c, and FPG from baseline to week 32 were analyzed using a paired
α-test. The Wilcoxon signed rank test was used to analyze the change in the number of hypoglycemic events from baseline to week 32.

**Results**

**Patient characteristics**

Overall, 747 patients were enrolled in the study, of which 686 patients (91.8%); 373 male and 311 female) were exposed to IDet and constituted the FAS. A total of 640 patients (85.7%) completed the study, while 107 patients (14.3%) discontinued from the study due to loss of contact (28 patients, 3.7%), ADRs (1 patient, 0.1%), and other reasons (78 patients, 10.4%).

At baseline, age (mean ± SD), body mass index (BMI), and diabetes duration for the cohort were 51.3 ± 11.0 years, 31.3 ± 5.5 kg/m², and 10.2 ± 6.1 years, respectively (Table 1).

Physicians opted to start IDet therapy to improve glycemic control in the majority of patients (93.0%). The other most common reasons were to reduce blood glucose variability (37.6%) and change due to insulin pen (34.2%).

**Other glucose-lowering therapy**

Prior to enrollment in the study, the majority of patients were on OGLDs only (380 patients, 55.8%), followed by OGLD + insulin therapy (209 patients, 30.7%) (Table 2). After enrolling in the study, the most common treatment regimen at baseline was OGLD + insulin therapy (611 patients, 89.1%), which remained relatively unchanged throughout the study.

The use of OGLDs among patients did not change markedly before and after enrollment and at the end of the study, with biguanides, sulfonylureas, and thiazolidinediones being the most common OGLDs used (reported at week 32 in 83.0%, 59.9%, and 17.2% of patients, respectively) [Table 3]. Details on the frequency of insulin injections by week are provided in Supplementary Table S1. Before enrolment, commonly used other insulin therapy included human premix insulin twice daily (50.5% of the patients), insulin glargine once daily (20.2% of the patients), NPH insulin twice daily (15.2% of the patients), and human soluble insulin twice daily and thrice daily (9.8% and 8.4% of the patients, respectively).

**Insulin detemir dose and frequency of administration**

The mean total daily dose of IDet was 32.0 ± 32.8 U at baseline, 38.7 ± 41.6 U at week 16, and 44.7 ± 60.7 U at week 32. By body weight, the mean daily dose of IDet was 0.4 ± 0.4 U/kg at baseline, 0.5 ± 0.5 U/kg at week 16, and 0.5 ± 0.6 U/kg at week 32.

| Table 1: Demographic and baseline characteristics |
|-----------------------------------------------|
| Parameters | Gulf cohort |
| n       | 686 |
| Sex, male/female (%) | 54.5/45.5 |
| Age (years) | 51.3±11.0 |
| Body weight (kg) | 85.5±15.7 |
| BMI (kg/m²) | 31.3±5.5 |
| Diabetes duration (years) | 10.2±6.1 |

| Table 2: Summary of other glucose-lowering therapy |
|-----------------------------------------------|
| Antidiabetic therapy, n (%) | Week 0 (prestudy) | Week 0 (new) | Week 16 | Week 32 |
| n       | 681 | 686 | 664 | 640 |
| OGLD only | 380 (55.8) | 0 (0.0) | 11 (1.7) | 2 (0.3) |
| OGLD and insulin | 209 (30.7) | 611 (89.1) | 584 (88.0) | 579 (90.5) |
| Premix insulin only | 55 (8.1) | 0 (0.0) | 1 (0.2) | 2 (0.3) |
| Basal and bolus insulin only | 22 (3.2) | 44 (6.4) | 40 (6.0) | 33 (5.2) |
| Basal insulin only | 4 (0.6) | 27 (3.9) | 25 (3.8) | 22 (3.4) |
| Bolus insulin only | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Other therapy | 0 (0.0) | 4 (0.6) | 2 (0.3) | 0 (0.0) |
| No therapy | 10 (1.5) | 0 (0.0) | 1 (0.2) | 1 (0.2) |

Calculation of percentages is based on the number of patients with nonmissing values (n). OGLDs included biguanides, sulfonylureas, thiazolidinediones, and acarbose. Patients could have been on more than 1 OGLD during the study. Insulin therapy other than insulin detemir included human soluble insulin, neutral protamine Hagedorn insulin, human premix insulin, and insulin glargine. OGLDs: Oral glucose-lowering drugs.

| Table 3: Summary of oral glucose-lowering therapy by week |
|-----------------------------------------------|
| OGLD, n (%) | Week 0 (prestudy) | Week 0 (new) | Week 16 | Week 32 |
| n       | 661 | 656 | 645 | 629 |
| Biguanides | 545 (82.5) | 535 (81.6) | 540 (83.7) | 522 (83.0) |
| Sulfonylurea | 447 (67.6) | 416 (63.4) | 403 (62.5) | 377 (59.9) |
| Thiazolidinediones | 164 (24.8) | 134 (20.4) | 114 (17.7) | 108 (17.2) |
| Acarbose | 21 (3.2) | 15 (2.3) | 15 (2.3) | 12 (1.9) |
| No OGLD | 68 (10.3) | 45 (6.9) | 50 (7.8) | 49 (7.8) |

Calculation of percentages is based on the number of patients with nonmissing values (n). A patient could have been on more than one oral glucose-lowering drug during the study. OGLD: Oral glucose-lowering drug.

After enrollment, the majority of patients injected IDet once daily (88.9%, 87.8%, and 87.5% at baseline, week 16, and week 32, respectively) [Supplementary Table S1].

**Safety**

**Adverse drug reactions and adverse events**

No SADRs were reported during this study. One moderate ADR of drug hypersensitivity, considered probably related to the study drug, was reported during the study. The study drug was withdrawn, and the patient recovered from the ADR.

One death due to cardiorespiratory arrest was reported during the study and was considered unlikely to be related...
to the study drug. One SAE of senile dementia was reported in the same patient; the event was considered to be mild in severity and unlikely to be related to the study drug. No other AEs or SAEs were reported during the study.

**Hypoglycemia**

At baseline, 102 patients (14.9%) reported 435 events of hypoglycemia with an incidence rate of 0.1585 events/patient-year [Table 4]. By week 32, 79 patients (11.5%) reported 204 events of hypoglycemia (0.0743 events/patient-year).

The change in the number of hypoglycemic events from baseline to week 32 was statistically significant for total hypoglycemia (mean change: −0.34; P = 0.0115) and daytime hypoglycemia (mean change: −0.23; P = 0.0031).

By week 32, 5.4% of patients reported nocturnal hypoglycemia compared to 6.3% at baseline (0.0215 events/patient-year vs. 0.0492 events/patient-year, respectively). The mean change in nocturnal hypoglycemia from baseline to week 32 was −0.11; however, this difference was not statistically significant.

At baseline, 17 patients (2.5%) reported major hypoglycemia, of which 9 patients (1.3%) reported 11 major nocturnal hypoglycemic events. No major hypoglycemic events were reported at week 32.

**Effectiveness**

**Body weight**

The mean body weight decreased from 85.7 ± 15.2 kg at baseline to 85.4 ± 14.5 kg at week 32 (mean change: −0.3 ± 2.66 kg; P = 0.0203) [Figure 1].

**Glycemic control**

By week 32, the mean HbA1c significantly improved to 7.7 ± 1.36% compared to 9.9 ± 1.67% at baseline (mean change: −2.2 ± 1.74%, P < 0.0001) [Figure 1].

The mean FPG significantly decreased from 11.9 ± 3.27 mmol/L at baseline to 7.4 ± 1.85 mmol/L at week 32 (mean change: −4.5 ± 3.39 mmol/L; P < 0.0001) [Figure 1].

**Discussion**

This 32-week study demonstrated the safety and effectiveness of IDet in treating patients with T2DM under normal clinical practice conditions in the Gulf countries. The results of this study supported the findings from previous randomized controlled trials regarding the safety and effectiveness of IDet therapy.[10,11,14-16]

With the progression of T2DM, supplementing OGLDs with insulin is essential to bolster endogenous insulin levels and maintain adequate glycemic control;[19] however, in this study, it appeared that many patients were not receiving or maintaining glucose-lowering therapy suited to their needs. At baseline, glycemic levels in this cohort (mean HbA1c level: 9.9 ± 1.67%; FPG: 11.9 ± 3.27 mmol/L) considerably exceeded the recommended level of <7.0% for HbA1c and <7.2 mmol/L for FPG specified by the ADA-EASD joint guidelines.[4] Although the mean duration of diabetes was 10.2 ± 6.1 years, over half of the patients (55.8%) were on OGLDS only. Improvement of glycemic control was cited as the primary reason for starting IDet therapy by 93% of physicians. These data emphasize the vital need to improve patient and physician awareness of T2DM management strategies and to ensure consistent implementation of treatment guidelines.

IDet therapy appeared to be well tolerated in the cohort with no SADRs and a low incidence of hypoglycemic events. There were no major hypoglycemic events reported at week 32. Moreover, the decrease in the number of total and daytime hypoglycemic events and the low number of nocturnal events by the end of the study also support the findings from randomized controlled trials that IDet therapy
does not exacerbate the incidence of hypoglycemia.[10,11,14-16]

One death (due to cardiorespiratory arrest) was reported in this study and was assessed as unlikely to be related to the trial drug.

Significant improvements in the mean HbA1c level (by −2.2%) and FPG level (by −4.5 mmol/L) were noted by week 32. However, the mean HbA1c and FPG levels at week 32 were still slightly above the levels recommended by the joint ADA-EASD guidelines.[4] The mean IDet dose was 44.7 ± 60.7 U by the end of the study, and 88% of patients were on IDet once daily by week 32. Only a small proportion of patients (~5%) were on basal-bolus insulin therapy at week 32, providing ample opportunities for further therapy intensification. It is likely that physicians favored a more cautious approach when initiating IDet therapy. Nevertheless, the low number of hypoglycemic events seen in the cohort, coupled with the absence of any unexpected safety findings, suggests that physicians could consider further intensification of therapy to attain the recommended glycemic levels.

Body weight gain associated with insulin therapy is one of the key barriers to patient compliance in T2DM management.[6] The mean body weight and BMI at baseline were noted to be high in this population (85.5 ± 15.7 kg and 31.3 ± 5.5 kg/m², respectively). In this cohort, a small, statistically significant decrease in the mean body weight was noted after 32 weeks (by −0.3 ± 2.66 kg). Therapy with IDet has consistently been associated with low body weight gain and even weight loss in other large observational studies such as PREDICTIVE and A1chieve.[12,13] Randomized, controlled clinical trials have also demonstrated lower weight gain with IDet in comparison with other basal insulins such as NPH insulin and insulin glargine.[14,16] Various theories have been propounded to explain the weight-limiting effect of IDet therapy; however, the exact mechanism is yet to be satisfactorily explained.[20] Many patients with T2DM snack frequently due to fear of hypoglycemia, leading to weight gain. It is possible that the low glycemic variability observed with IDet curtails defensive eating, resulting in weight loss. Another possible explanation is that albumin-bound IDet could induce a greater hepatic insulin effect, thereby reducing insulin activity and fat storage in the peripheral tissues. It has also been suggested that IDet could play a role in suppressing appetite by influencing satiety signaling in the brain.[20] In the current study, no information was collected regarding any modifications made in the patients’ lifestyle or diet, and it is possible that changes thereof could also have had an impact on body weight.

Limitations existed in this study due to the lack of randomization, absence of a control group and possible recall bias in the reporting of hypoglycemia as it was based on the patient’s recollection of hypoglycemic events.
occuring during the preceding 4 weeks. Furthermore, the results from statistical tests are only guiding in nature due to the possibility of bias and confounding in data. Data interpretation is further limited by the lack of information on possible diet and lifestyle changes and concomitant medications apart from OGLDs or insulin. It is usually observed that physicians recommend dietary and lifestyle modifications along with antidiabetic medications in T2DM patients; these modifications can, in turn, result in beneficial effects on glycemic and extraglycemic factors in these patients.[21,22] T2DM is a complex disease characterized by the development of macrovascular and microvascular disorders that frequently require multiple medications to be administered in combination.[23] The study included any patient starting IDet therapy, irrespective of previous treatment, and the average duration of diabetes was 10.2 years; therefore, patients in this study could have been on several other therapies during the duration of the study. However, data on concomitant medications apart from OGLDs or insulin were not captured in this study. Furthermore, the data recorded on other glucose-lowering drugs did not include the exact dosage and timing of administration of these medications. Hence, the precise effects of these factors in combination with IDet therapy could not be assessed in the current study. Nonetheless, this study provided the opportunity to evaluate the safety profile of IDet under normal clinical conditions in insulin-naive and insulin-experienced patients with T2DM in the Gulf region. In addition, the reduction in body weight seen with IDet could potentially be a favorable differentiator to improve patient adherence, which is a major challenge in the acceptance of insulin therapy. The findings from this postauthorization safety study could, therefore, be useful in providing guidance for the management of T2DM in clinical practice in this region.

**CONCLUSION**

The current study demonstrated that IDet therapy appeared to be well-tolerated with a low risk of hypoglycemia and improved glycemic control over 32 weeks in patients with uncontrolled T2DM on OGLDs or other insulins in the Gulf region. Continued dose optimization and treatment intensification could further enhance the therapeutic effects observed in this study.

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**Conflicts of interest**

Waleed AbdelFattah is employed by Novo Nordisk.

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Supplementary Table 1: Summary of daily insulin injections by week

|                     | Week 0 (pre-study) | Week 0 (new) | Week 16 | Week 32 |
|---------------------|-------------------|--------------|----------|---------|
| **N**               | 297               | 686          | 654      | 638     |
| **Insulin detemir, n (%)** |                   |              |          |         |
| 1 injection         | 0 (0.0)           | 610 (88.9)   | 574 (87.8) | 558 (87.5) |
| 2 injections        | 0 (0.0)           | 73 (10.6)    | 75 (11.5)  | 78 (12.2) |
| 3 injections        | 0 (0.0)           | 1 (0.1)      | 0 (0.0)   | 0 (0.0)  |
| 4 injections        | 0 (0.0)           | 2 (0.3)      | 1 (0.2)   | 0 (0.0)  |
| 5 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| **Human soluble insulin, n (%)** |                   |              |          |         |
| 1 injection         | 5 (1.7)           | 16 (2.3)     | 13 (2.0)  | 18 (2.8) |
| 2 injections        | 29 (9.8)          | 22 (3.2)     | 27 (4.1)  | 22 (3.4) |
| 3 injections        | 25 (8.4)          | 58 (8.5)     | 58 (8.9)  | 59 (9.2) |
| 4 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 5 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| **Neutral protamine Hagedorn insulin, n (%)** |                   |              |          |         |
| 1 injection         | 25 (8.4)          | 0 (0.0)      | 1 (0.2)   | 0 (0.0)  |
| 2 injections        | 45 (15.2)         | 4 (0.6)      | 2 (0.3)   | 3 (0.5)  |
| 3 injections        | 1 (0.3)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 4 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 5 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| **Human premix insulin, n (%)** |                   |              |          |         |
| 1 injection         | 9 (3.0)           | 8 (1.2)      | 7 (1.1)   | 7 (1.1)  |
| 2 injections        | 150 (50.5)        | 3 (0.4)      | 5 (0.8)   | 3 (0.5)  |
| 3 injections        | 1 (0.3)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 4 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 5 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| **Insulin glargine, n (%)** |                   |              |          |         |
| 1 injection         | 60 (20.2)         | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 2 injections        | 2 (0.7)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 3 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 4 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |
| 5 injections        | 0 (0.0)           | 0 (0.0)      | 0 (0.0)   | 0 (0.0)  |

Calculation of percentages is based on the number of patients with non-missing values (N). Three patients with more than 3 injections of insulin detemir per day were considered to be outliers.