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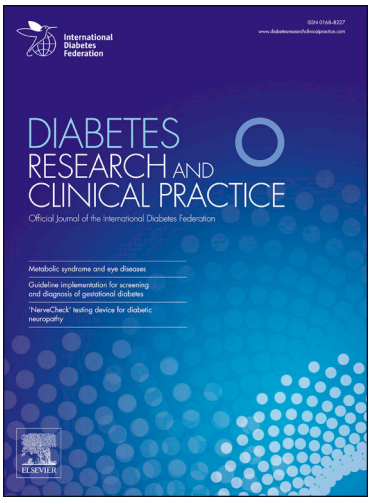

Switching to a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) is associated with improved glycaemic control in a real-world population with type 2 diabetes mellitus in the United Arab Emirates: *Results from the multicentre, prospective INTENSIFY study*

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PII: S0168-8227(22)00997-4
DOI: https://doi.org/10.1016/j.diabres.2022.110183
Reference: DIAB 110183

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 22 August 2022
Revised Date: 1 November 2022
Accepted Date: 18 November 2022

Please cite this article as: S. Abusnana, F. Al Awadi, H. Aly, A. Bashier, D. Kumar Dhanwal, T. Halasa, M. Jallo, J. Medina, S. Singhal, Switching to a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) is associated with improved glycaemic control in a real-world population with type 2 diabetes mellitus in the United Arab Emirates: *Results from the multicentre, prospective INTENSIFY study*, *Diabetes Research and Clinical Practice* (2022), doi: https://doi.org/10.1016/j.diabres.2022.110183

Switching to a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) is associated with improved glycaemic control in a real-world population with type 2 diabetes mellitus in the United Arab Emirates: *Results from the multicentre, prospective INTENSIFY study*

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Journal: Diabetes Research and Clinical Practice
Running title: INTENSIFY: IDegLira in real-world T2DM patients in the UAE
Word count: 4936 (limit 5000 words excluding references and abstract)
Number of figures/tables: 3/2

Abstract (current word count: 227; maximum 200)

Aim: Investigate the effectiveness of IDegLira, a fixed-ratio combination of insulin degludec/liraglutide, in a real-world setting in patients with type 2 diabetes mellitus in the United Arab Emirates.

Methods: This non-interventional study enrolled adults switching to IDegLira from basal insulin (BI) or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with/without concomitant oral antidiabetic drugs (OADs). Primary endpoint was change in HbA1c from baseline, assessed using a mixed model for repeated measurements.

Results: Among 263 patients (BI ± OADs, n=206; GLP-1 RA ± OADs, n=57), mean baseline HbA1c was 9.29% (78 mmol/mol). After 26 weeks, HbA1c was significantly reduced (BI ± OADs, –0.83% [–9.0 mmol/mol] and GLP-1 RA ± OADs, –1.24% [–13.5 mmol/mol]; both p<0.0001). Fasting plasma glucose (FPG) was significantly reduced (–39.48 mg/dL [BI ± OADs] and –82.49 mg/dL [GLP-1 RA ± OADs]; both p<0.0001). Before treatment initiation, 3/263 patients experienced ≥1 severe hypoglycaemic episode and 7/263 patients experienced ≥1 non-severe hypoglycaemic episode compared with 1/263 patients who had ≥1 severe and 1/263 who had ≥1 non-severe episode at end of study. Body weight decreased significantly among patients switching from BI ± OADs (–1.05 kg [p<0.0001]). Treatment was well tolerated.

Conclusions: IDegLira significantly reduced HbA1c and FPG in this real-world setting, along with less frequent episodes of hypoglycaemia. Switching to IDegLira offers effective treatment intensification for type 2 diabetes patients with inadequate glycaemic control.

Keywords: Glycaemic control; IDegLira; Observational study; real world; Type 2 diabetes; United Arab Emirates

1. Introduction

In type 2 diabetes mellitus (T2DM), the main goal of treatment is to maintain the patient's blood glucose at levels that correlate with individualized target levels of glycated haemoglobin (HbA1c) in order to improve outcomes and reduce both complications and mortality [1-4]. As diabetes is a progressive disease, maintaining these glycaemic targets usually requires a stepwise intensification of glucose-lowering treatments [5] that progress from initiation of metformin to the sequential addition of other oral antidiabetic drugs (OADs), followed by injectable therapy (basal insulin [BI], glucagon-like peptide-1 receptor agonists [GLP-1 RAs], or a combination of BI and GLP-1 RA administered either separately or in fixed combinations) [6-9]. Despite these measures, glycaemic control remains suboptimal in many patients in clinical practice, even in those who have progressed to injectable treatment [1,10]. Effective treatment-intensification strategies are therefore required to address the progressive nature of T2DM [11].

IDegLira is a fixed-ratio combination of insulin degludec and liraglutide, developed as a once-daily injection for the management of patients with inadequately controlled T2DM [12-15]. The effectiveness of IDegLira in reducing blood glucose levels has been demonstrated in the extensive, phase 3 Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes (DUAL) clinical trial programme, which enrolled patients with T2DM uncontrolled on basal insulin (DUAL II, V, VII) [16-18], GLP-1 RAs (DUAL III) [19], or OADs (DUAL I, IV, VI, VIII, IX) [13,20-23]. Data from several real-world studies [24-31] support those from the clinical trial programme [13,16-23], highlighting the generalisability of the clinical trial results to routine practice and providing important, country-specific clinical evidence.

In the United Arab Emirates (UAE), the national age-adjusted prevalence of diabetes is very high at 16.4% [32], and the associated morbidity and mortality place a huge burden on the health care system. IDegLira was launched in the UAE in 2018 for use in T2DM when OADs, either alone or in combination with BI or GLP-1 RAs, do not provide adequate glycaemic control. To date, however, neither clinical trials nor real-world studies have been conducted with IDegLira in this country.

The aim of the INTENSIFY study was to evaluate the effect of IDegLira on glycaemic control and other clinical parameters when used according to local clinical practice in the UAE in a real-world population of patients with T2DM inadequately controlled on BI or GLP-1 RAs, with or without OADs.

2. Materials and methods

2.1. Study design and population

INTENSIFY was an observational, prospective, non-interventional, open-label, real-world study (NCT03823339) conducted at 31 sites in the UAE between January 2019 and December 2020.

Patients were eligible for inclusion if they were aged ≥ 18 years with a clinical diagnosis of T2DM, and if they had inadequate glycaemic control (as evaluated by the treating physician) after receiving treatment with BI ± OADs or GLP-1 RA ± OADs for ≥ 12 weeks. All patients had to have available and documented values for HbA1c ≤ 12 weeks prior to the initiation of IDegLira treatment, and the decision to initiate IDegLira treatment was at the treating physician's discretion, made independently of the decision to enrol the patient in the study. Patients were excluded from the study if they had previously been treated with IDegLira, if they had known or suspected hypersensitivity to insulin degludec, liraglutide, or any of the excipients, or if they had any mental incapacity, unwillingness or language barriers that precluded adequate understanding or cooperation. Women who were pregnant, breastfeeding, or intending to become pregnant were also excluded.

The study duration was 26–38 weeks and consisted of a baseline visit, optional intermediate visits, and an end-of-study (EOS) visit (**Fig. 1**). Throughout the study, visit frequency followed the local standard of care and patients were treated with IDegLira according to routine clinical practice at the discretion of the treating physician, in accordance with the IDegLira label in the UAE. The starting dose of IDegLira, and any dose-step adjustments thereafter, were determined by the treating physician. As this was an observational study, physicians and their patients were free to intensify treatment when they wished to do so. Changes in glucose-lowering medications (including IDegLira) throughout the study were also permitted at the treating physician's discretion.

Patient diaries were not used in the INTENSIFY study. Instead, data related to clinical outcomes (other than laboratory measurements) were based on patient recollection and reported during visits, an approach that reflects local routine clinical practice. Data were collected until EOS for all patients, including those who discontinued treatment with IDegLira (unless consent was withdrawn). Body weight, IDegLira dose, HbA1c, and fasting plasma glucose (FPG) were collected as part of routine clinical practice and the most recent test results were recorded by the physician at each study visit. Data on the frequency of non-severe, non-severe nocturnal, and severe hypoglycaemic episodes before and after the initiation of IDegLira treatment were based on self-reported patient recollection at baseline and EOS (or discontinuation). Patients' treatment preferences (IDegLira vs. previous treatment) were assessed at EOS/discontinuation.

The study was conducted in accordance with the Declaration of Helsinki [33] and the Guidelines for Good Pharmacoepidemiology Practices [34], and informed consent was obtained from all patients prior to study commencement. All relevant independent ethics committees and institutional review boards reviewed and approved the study.

2.2. Endpoints

The primary endpoint was the change in HbA1c from baseline to EOS. A secondary endpoint relating to glycaemic control was change in FPG from baseline. Other secondary endpoints included the proportion of patients reaching an HbA1c level of < 7% (< 53 mmol/mol) by EOS, IDegLira dose steps throughout the study, change in body weight from baseline, and change in the number of patient-reported hypoglycaemic episodes (based on the number of episodes occurring within 4 weeks prior to EOS/discontinuation versus 4 weeks prior to initiation of IDegLira treatment [non-severe and non-severe nocturnal episodes] and the number of episodes occurring within 26 weeks prior to EOS/discontinuation versus the 26-week period prior to IDegLira initiation [severe episodes]). Treatment preference was assessed as an exploratory endpoint by asking patients the following questions: Are you willing to continue with IDegLira? Do you prefer IDegLira over your previous treatment?

The safety of IDegLira treatment was also assessed by systematically collecting information on adverse events (AEs) and serious AEs (SAEs) throughout the study.

2.3. Statistical analyses

2.3.1. Sample size

The primary endpoint (mean change in HbA1c from baseline) was used for sample size calculations. Separate calculations were performed for the two previous treatment subgroups (BI ± OADs and GLP-1 RA ± OADs) to have sufficient power for analysis of the secondary endpoint of patients achieving HbA1c < 7% (< 53 mmol/mol) at EOS.

For the primary endpoint, the sample size calculation aimed to provide sufficient power for analysis in the two treatment subgroups (BI ± OADs and GLP-1 RA ± OADs). Based on UAE local practice, 50% of patients were assumed to have previously received BI ± OADs, with a mean of paired differences in HbA1c of 0.9% (10 mmol/mol) [24], and 50% were assumed to have been previously treated with GLP-1 RA ± OADs, with a mean of paired differences in HbA1c of 1.1% (12 mmol/mol) [24]. The standard deviation (SD) of the change in both groups was assumed to be 1.6, as this is the level of variation expected in real-world practice [24]. In total, 36 and 25 patients were required in the BI ± OADs and GLP-1 RA ± OADs groups, respectively, for 90% power at the subgroup level and 80% overall power in analysis of the primary endpoint.

Sample size calculation for the secondary endpoint of patients reaching HbA1c < 7% (< 53 mmol/mol) used data from the real-world European Xultophy Treatment Retrospective Audit (EXTRA) study [24]. In EXTRA, 37.6% and 31.6% of patients previously on BI ± OADs and GLP-1 RA ± OADs, respectively, had HbA1c < 7% (< 53 mmol/mol) at EOS; for patients who had discontinued IDegLira by EOS, it was assumed that the proportion of responders was similar to baseline (i.e., an adjusted EOS proportion of 36.1% [BI ± OADs] and 29.6% [GLP-1 RA ± OADs]). Therefore, assuming 20% missing data, the number of patients needed was approximately 160 in the BI ± OADs group and 59 in the GLP-1 RA ± OADs group.

2.3.2. Statistical methods

All endpoints were analysed separately for each treatment subgroup as well as the overall population, based on the full analysis set (FAS), which comprised all patients who provided informed consent and initiated treatment with IDegLira.

Descriptive statistics were used to summarize baseline demographics, patient characteristics, and safety information. Analysis of the primary endpoint (change in HbA1c from baseline), based on all patients who initiated IDegLira treatment and who had at least one post-baseline HbA1c measurement, was carried out using a mixed model for repeated measurements (MMRM) adjusted to the baseline covariates of age, sex, diabetes duration, HbA1c value, body mass index (BMI), and baseline treatment regimen. Study site was also included as a fixed effect to account for within-site correlation. To handle deviation from linearity, Time (day of sampling from baseline) and Time square were included as fixed effects. Furthermore, Patient and Time*patient were included as random effects, to correct for the patient effect and allow it to vary over time. A binary categorization (yes/no) was used to calculate the proportion (%) of patients who achieved an HbA1c of < 7% (< 53 mmol/mol) by EOS. Changes in FPG and body weight from baseline were analysed using an MMRM in the same manner as the primary endpoint. Analysis of the mean number of IDegLira dose steps was also performed using an MMRM and included all patients with at least one IDegLira dose.

For analysis of hypoglycaemic episodes, changes in patient-reported number of non-severe hypoglycaemia (defined as an episode with patient-reported symptoms and/or self-measured plasma glucose < 3.9 mmol/L [70 mg/dL]), non-severe nocturnal (defined as occurring between midnight and early morning [as perceived by the patient] and meeting criteria for a non-severe episode), and severe hypoglycaemia (defined as an episode of hypoglycaemia requiring assistance of another person to actively administer carbohydrate, glucagon or take other corrective action) episodes were recorded.

Additionally, an adjusted negative binomial regression model specifying a log-transformed follow-up time offset term was used to examine the incidence rate of overall non-severe, non-severe nocturnal, and severe hypoglycaemic events during the study recollection period and pre-study recollection

period. Finally, data on patients' treatment preferences were recorded as percentages in frequency tables.

Analyses of the primary endpoint, patients achieving HbA1c < 7% (< 53 mmol/mol), change in FPG, and change in body weight were based on the in-study observation period, which was defined as the time period during which patients were in the study, regardless of adherence to IDegLira treatment. This period started at the baseline visit and finished at EOS, withdrawal of informed consent, the last physician-patient contact, patient death, or closure of study site (whichever came first). IDegLira dose steps, hypoglycaemic episodes, and patients' treatment preferences were analysed using the on-treatment observation period, defined as the time period in which patients were considered treated with IDegLira. This period started at the date of IDegLira initiation and ended at the date of the last IDegLira treatment, EOS, withdrawal of informed consent, last patient-physician contact, patient death, or closure of study site (whichever occurred first). Data management and analysis was carried out in Statistical Analysis Software (SAS) Enterprise Guide 8.2 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided, with a significance level of 0.05.

3. Results

3.1. Baseline characteristics and demographics

A total of 263 patients were included in INTENSIFY and comprised the FAS; 206 patients were on BI ± OADs and 57 were on GLP-1 RA ± OADs at baseline. Of these 263 patients, 214 completed the study and 49 withdrew; the majority of withdrawals were due to the patient being lost to follow-up (37/263 [14.1%]), with only a small number of cases being caused by withdrawal of informed consent (5/263 [1.9%]) or "other" reasons, namely patient death or closure of study site (7/263 [2.7%]). Of the 26 patients who discontinued IDegLira treatment, only a minority discontinued because of AEs (5 [1.9%]) or insufficient glycaemic control (1 [0.4%]); the remaining patients discontinued due to "other" (13 [4.9%]) reasons, most commonly patient's preference (46%), followed by physician's preference (23%), or unknown (7 [2.7%]) reasons. Treatment discontinuation did not lead to withdrawal from the study.

In terms of visit schedule throughout the study, most patients (134 [51.0%]) had just one intermediate visit, and 32 (12.2%) and 4 (1.5%) had two or three visits, respectively. No patients had more than three intermediate visits, and 93 (35.4%) had no intermediate visits over the course of the study.

Baseline demographics and characteristics are summarised in **Table 1.** Overall, most patients were male (67.3%), the mean patient age was 51.9 years, and the mean duration of diabetes was 12.2 years. At baseline, the mean BMI was 30.5 kg/m^2 and the mean FPG was 206.6 mg/dL. The mean HbA1c in the overall population was 9.29% (78 mmol/mol), and 7 (2.7%) patients had an HbA1c of < 7% (< 53 mmol/mol). For most patients (255 [97.0%]), a key reason for initiating IDegLira treatment was to improve glycaemic control. Among patients who switched from treatment with BI ± OADs, the previous mean daily insulin dose was 30.4 IU; among those who switched from GLP-1 RA ± OADs, 30 had previously been on liraglutide (mean dose, 1.9 mg/day[1]) and 27 had previously received dulaglutide (mean dose, 1.5 mg/week). In both treatment subgroups, the most common concomitant antidiabetic medications were biguanides (76.2% and 86.0% of patients in the BI ± OADs and GLP-1 RA ± OADs groups, respectively) and sodium-glucose co-transporter 2 inhibitors (59.2% and 64.9%, respectively). The mean prescribed starting doses of IDegLira were 21.6 dose steps for patients previously on BI ± OADs and 18.6 dose steps for those previously treated with GLP-1 RA ± OADs.

3.2. Glycaemic control

Switching to treatment with IDegLira was associated with improvements in overall HbA1c control, including significant reductions in HbA1c in both treatment subgroups (**Fig. 2A**). According to the adjusted MMRM, the estimated mean HbA1c at EOS was 8.52% (standard error [SE], 0.14) or 70 mmol/mol (SE, 1.5) in patients switching from BI ± OADs, representing an estimated mean (SE) change from baseline of –0.83% (0.14) or –9 mmol/ml (1.5) ($p < 0.0001$). The reduction in HbA1c was greater in patients previously treated with GLP-1 RA ± OADs: in this patient subgroup, the mean (SE) HbA1c at EOS was 8.01% (0.19) or 64 mmol/mol (2.1), providing an estimated mean change from baseline of –1.24% (0.19) or –13.5 mmol/mol (2.1) ($p < 0.0001$).

[1] Note 1 patient reported to have received 6 mg/day liraglutide.

Treatment with IDegLira was also associated with significant reductions in FPG (**Fig. 2B**). At EOS, estimated mean (SE) FPG was 164.70 mg/dL (7.75) in the BI ± OADs group and 145.33 mg/dL (5.7) in the GLP-1 RA ± OADs group, representing reductions from baseline of –39.48 mg/dL (7.75) and -82.49 mg/dL (5.69), respectively (both $p < 0.0001$).

3.3. HbA1c < 7% (< 53 mmol/mol)

Among patients in the BI ± OADs group, 19 of the 206 patients (9.2%) who began IDegLira treatment achieved a HbA1c of < 7% (< 53 mmol/mol) at EOS. In the GLP-1 RA ± OADs group, 8 of the 57 patients (14.0%) who initiated IDegLira also reached a HbA1c of < 7% (< 53 mmol/mol).

3.4. IDegLira dose steps

Over the course of the study, IDegLira dose steps increased in both subgroups. Patients switching from BI ± OADs had an estimated mean (SE) IDegLira dose of 27.97 dose steps (0.62) at EOS; the mean (SE) estimated increase from baseline was 5.85 dose steps (0.62), 95% CI, 4.6 to 7.1. Among patients previously treated with GLP-1 RA ± OADs, the estimated mean (SE) dose of IDegLira at EOS was 26.49 dose steps (1.42), representing an increase of 6.94 dose steps (1.42), 95% CI, 4.0 to 9.8. The increase from baseline was statistically significant in both subgroups ($p < 0.0001$ for both).

3.5. Body weight

A significant reduction in body weight was achieved among patients switching from BI ± OADs: the estimated mean (SE) body weight in these patients was 80.67 kg (0.25) at EOS, representing an estimated reduction of –1.05 kg (0.25), 95% CI, –1.5 to –0.6 ($p < 0.0001$). There was a statistically significant increase in body weight among patients switching from GLP-1 RA ± OADs (estimated mean [SE] body weight at EOS, 95.85 kg [0.51]; estimated mean [SE] change from baseline, 1.25 kg [0.51], 95% CI, 0.2 to 2.3; $p = 0.0246$).

3.6. Hypoglycaemic episodes

The numbers of patients reporting at least one severe, non-severe, or non-severe nocturnal hypoglycaemic episode was numerically lower after IDegLira treatment than at baseline, although these differences did not reach statistical significance (**Fig. 3**). Estimated incidence rates for all three

types of hypoglycaemic episode were also numerically lower at EOS or discontinuation versus baseline (**Table 2**). However, while the estimated incidence rate ratios of overall severe, non-severe, and non-severe nocturnal hypoglycaemic episodes (0.50, 0.18, and 0.37, respectively) all indicated a lower risk of hypoglycaemia following the switch to IDegLira, these rate ratios were not statistically significant (**Table 2**). The lack of statistical significance is likely due to the low frequency of these episodes.

3.7. Patient preference

Of 215 patients who provided information regarding treatment preferences, 185 (86%) were willing to continue with IDegLira treatment. Additionally, 185/215 patients (86%) preferred IDegLira over their previous treatment. The remaining 30 (14.0%) patients did not prefer IDegLira over their previous (or other) treatment.

3.8. Safety

Treatment with IDegLira was well-tolerated and there were no unexpected safety findings. A total of 20 patients (7.60%) experienced 37 AEs during the study; most AEs (21 [56.8%]) were mild in severity, while 10 (27.0%) were moderate and 6 (16.2%) were severe. The outcome for most of the reported AEs (34 [91.9%]) was recovered or resolved. IDegLira was withdrawn in five patients as a result of four non-serious AEs and one SAE. In total, 16 AEs in 12 patients were considered probably or possibly related to IDegLira.

There were eight SAEs in four patients, all of which were considered unlikely related to IDegLira treatment; one SAE in a 79-year-old female patient (“metastases to bone”) proved fatal, but all other SAEs resolved with (n = 1) or without (n = 6) sequelae. One SAE reported as hyperglycaemia in a 50-year-old female led to withdrawal of IDegLira, but the patient made a full recovery.

The most frequent safety AEs were related to the gastrointestinal and metabolic systems, but reported rates were still very low (14 events in 12 patients and 7 events in 4 patients, respectively). These AEs were more common among patients who switched from BI ± OADs (gastrointestinal AEs, 13 events in 11 patients; metabolic and nutritional AEs, 7 events in 4 patients [hypoglycaemia, 5

events in 2 patients; dehydration, 1 event in 1 patient; hyperglycaemia, 1 event in 1 patient]) than among those who switched from GLP-1 RA ± OADs (gastrointestinal AEs, 1 event in 1 patient; metabolic and nutritional AEs [hypoglycaemia, dehydration, hyperglycaemia], 0 events).

4. Discussion

The INTENSIFY study demonstrated that switching to IDegLira from either BI ± OADs or GLP-1 RA ± OADs was associated with improved glycaemic control in a real-world population of patients with T2DM in the UAE, as shown by significant reductions in HbA1c and FPG after approximately 26 weeks of treatment. This improvement in glycaemic control was accompanied by a reduction in the number of non-severe, nocturnal non-severe, and severe hypoglycaemic episodes. Body weight was also significantly reduced in patients who switched from BI ± OADs. Overall, a high proportion (86%) of patients expressed a preference for, and a willingness to continue with, IDegLira versus their previous treatment. This clearly demonstrates the potential of IDegLira when used in an intensification regimen for patients who need improved glycaemic control.

After 26 weeks of treatment with IDegLira, HbA1c was significantly reduced from baseline in the overall population and in patients switching from BI ± OADs or GLP-1 RA ± OADs (-0.91% [–10 mmol/mol], -0.83% [–9.0 mmol/mol], and -1.24% [-–13.5 mmol/mol], respectively). In the DUAL clinical trial programme, reductions in HbA1c at 26 or 32 weeks after initiating IDegLira were –1.5% (–16 mmol/mol) to –1.9% (–21 mmol/mol) among patients previously treated with BI + OADs (DUAL II, V, VII) [16-18], –1.3% (–14.5 mmol/mol) in patients on GLP-1 RA (DUAL III) [19], and between –1.5% (–16 mmol/mol) and –2.0% (–22 mmol/mol) among patients on various combinations of OADs (DUAL I, IV, VI, VIII, IX) [13,20-23]. Data from INTENSIFY align more closely with those derived from other real-world studies: in the pivotal EXTRA study, for example, patients on BI or GLP-1 RA (both ± OADs) at baseline achieved reductions in HbA1c of -0.9% (–10 mmol/mol) and -1.0% (–11 mmol/mol), respectively, after 26 weeks of IDegLira treatment [24]. Several more recent real-world studies investigating the effects of IDegLira treatment after 26 weeks found HbA1c reductions ranging from –0.8% to –1.1% (–9.0 to –12 mmol/mol) in patients on BI ± OADs at baseline and from –0.9% to –1.4% (–10 to –15.3 mmol/mol) in those on GLP-1 RA ± OADs [26-28].

Variations in study design, inclusion criteria, baseline HbA1c values, and dose escalation schedules account for many between-study differences in results [30], and this is especially relevant when comparing real-world results with data from clinical trials. In real-world studies, adherence may also be a key factor determining reduction in HbA1c. In INTENSIFY, for example, adherence was not monitored, and some patients may have been financing at least some aspects of treatment themselves, which may have impacted adherence. The smaller HbA1c reductions found in INTENSIFY (and other real-world studies) relative to the results obtained in clinical trials may also highlight the need for stricter dose titration in routine clinical practice. The recommended starting dose of IDegLira when switching patients from BI or GLP-1 RA is 16 dose steps (16 units of insulin degludec and 0.6 mg liraglutide), with twice-weekly dose titration to a daily maximum of 50 dose steps [14,15]. In INTENSIFY, although IDegLira was initiated at a mean starting dose of 21.6 and 18.6 dose steps in the BI ± OADs and GLP-1 RA ± OADs groups, respectively, the dose was never titrated beyond a mean of 28 dose steps in either subgroup. This real-world titration approach accounts for an overall change of 6.1 dose steps over the study period of 26–38 weeks, which roughly equates to just 1 dose step increase per month. Given the high baseline HbA1c level in many patients (overall mean, 9.29% [78 mmol/mol]), and the low frequency of hypoglycaemic events, a stricter titration schedule would be expected.

Several reasons can be speculated to explain the conservative titration approach seen in INTENSIFY. The first is the low level of interaction (and thus a reduced level of effective communication) observed between patients and physicians. Treatment guidelines recommend testing HbA1c every 3 months so that treatment can be intensified as necessary [3,35] to achieve target levels within 6 months [36]. Further, real-world data suggest that optimal patient management during IDegLira treatment in routine practice depends on relatively frequent patient-physician interaction (namely, three visits and two phone calls over a period of < 26 weeks) [37]. However, in routine practice in the UAE, patients may be followed-up less frequently (e.g., every 6 months). This may partially explain why 51% of patients had just one intermediate visit during INTENSIFY and why more than one-third (35.4%) had no intermediate visits at all. The level of interaction was also very likely impacted by the COVID-19 pandemic (which affected all trial sites); many patients may have wished to avoid interaction due to concerns about COVID-19 infection, and physicians were presumably less accessible due to an

increased COVID-19–related patient load. Irrespective of the reasons, however, it is likely that the lack of interaction between physicians and their patients contributed to the cautious titration approach. Mandating even one visit, by telephone if in-person contact was not feasible or desirable, may have resulted in more dose escalations and possibly greater HbA1c reductions. Additionally, a few physicians may have been concerned about strict dose titration, particularly in the case of patients with poor long-term glycaemic control or other complications necessitating a less aggressive titration approach. Another factor possibly affecting titration is that, when compared with other regions (such as the USA or UK), practical experience implies a relative lack of education and support available to patients in the UAE regarding appropriate diet and self-management. Many institutions, for example, do not have a dedicated diabetes nurse or educator to help patients control their diabetes. This means that patients do not always have adequate understanding about correct and appropriate dose intensification. As a result, some patients may lack motivation to frequently monitor their plasma glucose levels, or they may avoid dose titration due to concerns about hypoglycaemia, weight gain, or other potential side effects. Potential financial constraints may also hinder adequate dose titration, such as concerns about consultation fees and unavailability of (or limited access to) either IDegLira itself or glucometers/testing strips. Diabetes medications are mostly reimbursed in the UAE, although some patients may have lost insurance coverage (and therefore reimbursement) during the COVID-19 pandemic; further, while medications are covered under most regular health insurance plans, home glucose monitoring is not. It may be beneficial for the diabetes community to address some of these issues, as even greater improvements in glycaemic control than those seen in INTENSIFY may be achieved in the real-world setting with stricter, more aggressive IDegLira dose titration [24].

Switching to IDegLira treatment was also associated with less frequent hypoglycaemic episodes and, in the BI ± OADs group, a reduction in body weight. These positive effects on safety and efficacy can be attributed to the combination of BI with a GLP-1 RA; when these medications are co-administered, their different mechanisms of action work together, consequently reducing insulin-dose requirements and thus partially mitigating the risk of weight gain and lowering the risk of hypoglycaemia. While only relatively small proportions of patients reached an HbA1c of < 7% (< 53 mmol/mol) at EOS (9.2% and 14.0% in the BI ± OADs and GLP-1 RA ± OADs groups, respectively), achievement of this goal was

likely hindered by the low levels of interaction between patients and physicians (as described above), leading to inadequate dose titration.

INTENSIFY was a non-interventional study designed to reflect real-world experience with IDegLira in the UAE. This study was a real-world study designed to evaluate the effect of IDegLira on glycaemic control and other clinical parameters according to local clinical practice. The aim of this study was not to compare the effect of IDegLira between patients on basal insulin and GLPI-1 Ras, as such a study would require a different design and statistical analysis approach, e.g., enrolment of a greater and comparable number of patients per group. Study sites were selected based on their ability to enrol sufficient patients from different geographic locations in order to reflect the country's population, while eligible patients were those who were switching from BI or GLP-1 RAs (with or without OADs). Together, these inclusion criteria allowed for the enrolment of real-world patients with T2DM who are treated according to current clinical practice for patients who need treatment intensification, thus ensuring that the study results are generalizable to the broad population of patients with T2DM in the UAE for whom IDegLira treatment is indicated. It may also be possible to extrapolate the study results to other patient populations with similar characteristics. Finally, the study used primary data collection, whereby clinical data (except laboratory measurements) were obtained from patient recollections; this approach reflects real-world practice more accurately than the use of patient diaries and avoids the "diary fatigue" that is an inherent source of potential bias [38].

Some study limitations should also be noted, most of which are typical for observational studies. As this was a single-arm study, the absence of a comparator group means that alternative explanations for changes in endpoints from baseline cannot be evaluated or ruled out. Other limitations include the impact of potential confounders, which cannot be fully excluded (even though attempts were made to mitigate them by ensuring an unselected enrolment of sites and patients and by adjusting for all known confounders in statistical analyses), and the lack of control over parameter ranges and titration methods. As in all open-label studies, there may also be a risk of an underlying reporting bias. As data were collected through routine clinical practice rather than through mandatory assessments at prespecified time points, the completeness and robustness of study data may be impacted. Finally,

the results may be affected by differences in local clinical practice, insurance coverage patterns, and external circumstances (such as the COVID-19 pandemic).

In conclusion, results from the INTENSIFY study add to the growing body of real-world evidence supporting IDegLira as an effective intensification strategy for patients with T2DM previously treated with BI or GLP-1 RA (± OADs). Despite suboptimal dose titration and a lack of intermediate visits, switching to IDegLira treatment significantly reduced both HbA1c and FPG from baseline in both patient subgroups, and these significant improvements in glycaemic control were accompanied by a reduction in hypoglycaemic episodes. A reduction in body weight was also observed in patients switching from BI ± OADs. There were no unexpected safety findings or concerns, and more than 80% of patients preferred IDegLira to their previous treatment. Stricter titration guidelines and more frequent interactions between patients and investigators may have led to even greater improvements in glycaemic control and other endpoints.

Acknowledgements

The authors wish to thank the patients, investigators and CRO (MCT CRO) for their contributions to the study. We thank the following study investigators: Dr. Reyaz Ahmad, Dr. Ravi Arora, Dr. Sandeep Chaudhary, Dr. Asok Cheriyan, Dr. Mazhar Dalvi, Dr. Adel El-Naggar, Dr. Tariq Gul Shaikh, Dr. Vikram Hundia, Dr. Abdul Jabbar, Dr. Hadiah Kayiaseh, Dr. Asif Khan, Dr. Vani Krishna Warrier, Dr. Rakesh Kumar Khandelwal, Dr. Ajith Kumar, Dr. Dhafir Mahmood, Dr. Sameem Majid Matto, Dr. Mohamed Nabil Mahna, Dr. Maneesha Pandey, Dr. Aswin Pankajakshan, Dr. Srinivasa Rao Polumuru, Dr Fauzia Rashid, Dr Ahmed Saleh, Dr. Mona Salah El Din, Dr. Shenaz Seedat, Dr. Ibrahem Siam, Dr. Ihab El Tayeb, and Dr. Ajaz Yasmeen. Medical writing and editorial assistance were provided by Julie Smith PhD, and Sue Neville MSc of Parexel and funded by Novo Nordisk.

Funding

The INTENSIFY study was sponsored by Novo Nordisk.

Author contributions

S.S and H.A. were responsible for the study design and data interpretation. J.M. and T.H. developed the statistical analysis plan, were responsible for data interpretation and study analysis. S.A., F.A.A.,

A.B, D.K.D. and M.J. were study investigators and participated in data acquisition. All authors participated in critically analysing the obtained information and approved the final version of the manuscript.

Declaration of competing interest

A.B. has received honoraria for lectures from many companies including Novo Nordisk, AZ, MSD, Sanofi, Alhikma, Servier etc. M.K.J. has received research funds as PI from Sanofi, Novo Nordisk , Johnson & Johnson and MSD, and has received speaker honoraria as invited speaker in continuing medical education events from Sanofi, Novo Nordisk, Novartis, MSD. F.A. has received payment to PI and co-PI and research coordinator. S.A. has received payment or honoraria for lectures. D.K.D. has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, Novo Nordisk, Lilly, Abbott, MSD, Servier and Hikma Pharmaceuticals, and has received support for attending meetings and/or travel from AACE Community Dubai.

H.A. and S.S. are employees of Novo Nordisk UAE. T.H. and J.M. are employees of Novo Nordisk A/S, Søborg, Denmark.

REFERENCES

[1] Harris S, Abrahamson MJ, Ceriello A, Charpentier G, Evans M, Lehmann R, et al. Clinical considerations when initiating and titrating insulin degludec/liraglutide (IDegLira) in people with type 2 diabetes. Drugs 2020;80(2):147–65. doi: 10.1007/s40265-019-01245-3.

[2] Ostawal A, Mocevic E, Kragh N, Xu W. Clinical effectiveness of liraglutide in type 2 diabetes treatment in the real-world setting: a systematic literature review. Diabetes Ther 2016;7(3):411–38. doi: 10.1007/s13300-016-0180-0.

[3] American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1):S73–S84. doi: 10.2337/dc21-S006.

[4] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359(15):1577–89. doi: 10.1056/NEJMoa0806470.

[5] Moreira RO, Cobas R, Lopes Assis Coelho RC. Combination of basal insulin and GLP-1 receptor agonist: is this the end of basal insulin alone in the treatment of type 2 diabetes? Diabetol Metab Syndr 2018;1026. doi: 10.1186/s13098-018-0327-4.

[6] Hughes E. IDegLira: redefining insulin optimisation using a single injection in patients with type 2 diabetes. Prim Care Diabetes 2016;10(3):202–9. doi: 10.1016/j.pcd.2015.12.005.

[7] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41(12):2669–701. doi: 10.2337/dci18-0033.

[8] American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1):S111–S24. doi: 10.2337/dc21-S009.

[9] Alawadi F, Alsaeed M, Bachet F, Bashier A, Abdulla K, Abuelkheir S, et al. Impact of provision of optimum diabetes care on the safety of fasting in Ramadan in adult and adolescent patients with type 1 diabetes mellitus. Diabetes Res Clin Pract 2020;169:108466. doi: 10.1016/j.diabres.2020.108466.

[10] Fadini GP, Disoteo O, Candido R, Di Bartolo P, Laviola L, Consoli A. Delphi-based consensus on treatment intensification in type 2 diabetes subjects failing basal insulin supported oral treatment: focus on basal insulin + GLP-1 receptor agonist combination therapies. Diabetes Ther 2021;12(3):781–800. doi: 10.1007/s13300-021-01012-2.

[11] Vedtofte L, Knop FK, Vilsboll T. Efficacy and safety of fixed-ratio combination of insulin degludec and liraglutide (IDegLira) for the treatment of type 2 diabetes. Expert Opin Drug Saf 2017;16(3):387–96. doi: 10.1080/14740338.2017.1288715.

[12] Greig SL, Scott LJ. Insulin degludec/liraglutide: a review in type 2 diabetes. Drugs 2015;75(13):1523–34. doi: 10.1007/s40265-015-0448-0.

[13] Gough SCL, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol 2014;2(11):885–93. doi: 10.1016/s2213-8587(14)70174-3.

[14] Xultophy. [prescribing information]. 2019. https://www.novo-pi.com/xultophy10036.pdf. [accessed 15 December 2021].

[15] Xultophy. [summary of product characteristics]. 2020. https://www.medicines.org.uk/emc/medicine/29493. [accessed 15 December 2021].

[16] Buse JB, Vilsboll T, Thurman J, Blevins TC, Langbakke IH, Bottcher SG, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Care 2014;37(11):2926–33. doi: 10.2337/dc14-0785.

[17] Lingvay I, Perez Manghi F, Garcia-Hernandez P, Norwood P, Lehmann L, Tarp-Johansen MJ, et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. JAMA 2016;315(9):898–907. doi: 10.1001/jama.2016.1252.

[18] Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes

uncontrolled on metformin and basal insulin: the DUAL VII randomized clinical trial. Diabetes Care 2018;41(5):1009–16. doi: 10.2337/dc17-1114.

[19] Linjawi S, Bode BW, Chaykin LB, Courreges JP, Handelsman Y, Lehmann LM, et al. The efficacy of IDegLira (insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial. Diabetes Ther 2017;8(1):101–14. doi: 10.1007/s13300-016-0218-3.

[20] Rodbard HW, Bode BW, Harris SB, Rose L, Lehmann L, Jarlov H, et al. Safety and efficacy of insulin degludec/liraglutide (IDegLira) added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naive people with type 2 diabetes: the DUAL IV trial. Diabet Med 2017;34(2):189–96. doi: 10.1111/dme.13256.

[21] Harris SB, Kocsis G, Prager R, Ridge T, Chandarana K, Halladin N, et al. Safety and efficacy of IDegLira titrated once weekly versus twice weekly in patients with type 2 diabetes uncontrolled on oral antidiabetic drugs: DUAL VI randomized clinical trial. Diabetes Obes Metab 2017;19(6):858–65. doi: 10.1111/dom.12892.

[22] Sesti G, Bardtrum L, Dagdelen S, Halladin N, Haluzik M, Orsy P, et al. A greater proportion of participants with type 2 diabetes achieve treatment targets with insulin degludec/liraglutide versus insulin glargine 100 units/mL at 26 weeks: DUAL VIII, a randomized trial designed to resemble clinical practice. Diabetes Obes Metab 2020;22(5):873–8. doi: 10.1111/dom.13957.

[23] Philis-Tsimikas A, Billings LK, Busch R, Portillo CM, Sahay R, Halladin N, et al. Superior efficacy of insulin degludec/liraglutide versus insulin glargine U100 as add-on to sodium-glucose co-transporter-2 inhibitor therapy: a randomized clinical trial in people with uncontrolled type 2 diabetes. Diabetes Obes Metab 2019;21(6):1399–408. doi: 10.1111/dom.13666.

[24] Price H, Bluher M, Prager R, Phan TM, Thorsted BL, Schultes B, et al. Use and effectiveness of a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) in a real-world population with type 2 diabetes: results from a European, multicentre, retrospective chart review study. Diabetes Obes Metab 2018;20(4):954–62. doi: 10.1111/dom.13182.

[25] Sofra D. Glycemic control in a real-life setting in patients with type 2 diabetes treated with IDegLira at a single Swiss center. Diabetes Ther 2017;8(2):377–84. doi: 10.1007/s13300-017-0234-y.

[26] Melzer-Cohen C, Chodick G, Naftelberg S, Shehadeh N, Karasik A. Metabolic control and adherence to therapy in type 2 diabetes mellitus patients using IDegLira in a real-world setting. Diabetes Ther 2020;11(1):185–96. doi: 10.1007/s13300-019-00725-9.

[27] Egede LE, Bogdanov A, Fischer L, Da Rocha Fernandes JD, Kallenbach L. Glycemic control among patients newly prescribed IDegLira across prior therapy group in US real-world practice. Diabetes Ther 2020;11(7):1579–89. doi: 10.1007/s13300-020-00850-w.

[28] Di Loreto C, Celleno R, Piastrella L, Del Sindaco P. IDegLira fixed-ratio combination in the real world: a retrospective observational single-center Italian experience. Eur Rev Med Pharmacol Sci 2020;24(20):10671–9. doi: 10.26355/eurrev_202010_23425.

[29] Eliasson B, Ekelund J, Miftaraj M, Ranthe MF, Mardby AC, Da Rocha Fernandes JD, et al. Persistence with IDegLira in patients in clinical practice: a nationwide observational study in Sweden. Diabetes Ther 2020;11(8):1807–20. doi: 10.1007/s13300-020-00872-4.

[30] Persano M, Nollino L, Sambataro M, Rigato M, Negro I, Marchetto S, et al. Real-world study on the effectiveness and safety of basal insulin IDegLira in type 2 diabetic patients previously treated with multi-injective insulin therapy. Eur Rev Med Pharmacol Sci 2021;25(2):923–31. doi: 10.26355/eurrev_202101_24661.

[31] Zenari L, Da Porto A, De Moliner L, Lugli F, Guazzoni V, Groppelli G, et al. Real-World evaluation of glycemic outcomes and extra-glycemic parameters in diabetic patients treated with the combined formulation degludec-liraglutide (IDegLira). Diabetes Ther 2021;12(1):197–209. doi: 10.1007/s13300-020-00945-4.

[32] International Diabetes Federation. IDF Diabetes Atlas, 10th edn 2021. https://www.diabetesatlas.org. [accessed 4 January 2022].

[33] World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 2004. https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2004.pdf. [accessed 10 March 2022].

[34] International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP). 2015. https://www.pharmacoepi.org/resources/policies/guidelines-08027/. [accessed 10 March 2022].

[35] Alawadi F, Abusnana S, Afandi B, Aldahmani KM, Alhajeri O, Aljaberi K, et al. Emirates Diabetes Society Consensus guidelines for the management of type 2 diabetes mellitus – 2020. Dubai Diabetes Endocrinol J 2020;26(1):1-20. doi: 10.1159/000506508.

[36] Deed G, Barlow J, Kuo I. Early and tight glycaemic control - the key to managing type 2 diabetes. Aust Fam Physician 2012;41(9):681-4.

[37] Drummond R, Baru A, Dutkiewicz M, Basse A, Tengmark BO. Physicians' real-world experience with IDegLira: results of a European survey. BMJ Open Diabetes Res Care 2018;6(1):e000531. doi: 10.1136/bmjdrc-2018-000531.

[38] Fadini GP, Feher M, Hansen TK, de Valk HW, Koefoed MM, Wolden M, et al. Switching to degludec from other basal insulins is associated with reduced hypoglycemia rates: a prospective study. J Clin Endocrinol Metab 2019;104(12):5977–90. doi: 10.1210/jc.2019-01021.

Figure Legends

Fig. 1. Study design.

FAS, full analysis set; GLP-1 RA, glucagon-like peptide-1 receptor agonists; OADs, oral antidiabetic drugs; T2DM, type 2 diabetes mellitus.

Fig. 2. Change from baseline in (A) HbA1c and (B) FPG.

Data are estimated mean change (95% CI) in (A) HbA1c and (B) FPG. *p < 0.0001, based on adjusted mixed models for repeated measures.

BI, basal insulin; CI, confidence interval; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; OADs, oral antidiabetic drugs.

Fig. 3. Hypoglycaemic episodes.

BI, basal insulin; EOS, end of study; GLP-1 RA, glucagon-like peptide-1 receptor agonists; OADs, oral antidiabetic drugs.

[a] 4 weeks (non-severe and non-severe nocturnal episodes) or 26 weeks (severe episodes) prior to IDegLira initiation. [b] 4 weeks (non-severe and non-severe nocturnal episodes) or 26 weeks (severe episodes) prior to EOS or discontinuation.

Table 1 Baseline demographics and characteristics.

Characteristic	Overall	BI ± OADs	GLP-1 RA ± OADs
Full analysis set, n	263	206	57
Sex, n (%)			
Female	86 (32.7)	65 (31.6)	21 (36.8)
Male	177 (67.3)	141 (68.4)	36 (63.2)
Age, years	51.9 (11.1)	52.8 (11.2)	48.7 (10.2)
HbA1c, %	9.29 (1.6)	9.35 (1.7)	9.07 (1.4)
HbA1c, mmol/mol	78.0 (18.0)	78.7 (18.7)	75.7 (15.0)
HbA1c category, n (%)			
< 7% [< 53 mmol/mol]	7 (2.7)	6 (2.9)	1 (1.8)
7 – < 8.5% [53 – < 69.4 mmol/mol]	84 (31.9)	64 (31.1)	20 (35.1)
8.5 – < 10% [69.4 – < 85.8 mmol/mol]	99 (37.6)	75 (36.4)	24 (42.1)
≥ 10% [≥ 85.8 mmol/mol]	73 (27.8)	61 (29.6)	12 (21.1)
FPG, mg/dL	206.6 (92.0)	202.5 (92.5)	220.8 (89.8)
Body weight, kg	84.8 (16.6)	82.1 (15.4)	94.9 (17.4)
BMI, kg/m^2	30.5 (5.3)	29.6 (4.9)	33.8 (5.5)
Duration of diabetes, years	12.2 (6.6)	12.9 (6.6)	9.9 (5.8)
IDegLira starting dose (dose steps)	20.9 (8.8)	21.6 (9.3)	18.6 (6.1)
Reasons for initiating IDegLira treatment, n (%)[a]			
Improve glycaemic control	255 (97.0)	198 (96.1)	57 (100.0)
Hypoglycaemia	8 (3.0)	8 (3.9)	0
Convenience	48 (18.3)	40 (19.4)	8 (14.0)

Characteristic	Overall	BI ± OADs	GLP-1 RA ± OADs
Other	33 (12.5)	28 (13.6)	5 (8.8)
Daily dose of previous BI, IU/day	30.4 (14.0)	30.4 (14.0)	—
Dose of previous GLP-1 RA			
Liraglutide, mg/day	1.9[b] (0.8)	—	1.9 (0.8)
Dulaglutide, mg/week	1.5 (0.1)	—	1.5 (0.1)
Patients with hypoglycaemic episodes, n (%)			
Non-severe[c]	7 (2.7)	7 (3.4)	0
Non-severe nocturnal[c]	5 (1.9)	5 (2.4)	0
Severe[d]	3 (1.1)	1 (0.5)	2 (3.5)
Patients with diabetes complications, n (%)			
Cardiovascular disease	32 (12.2)	26 (12.6)	6 (10.5)
Diabetic retinopathy	34 (12.9)	31 (15.0)	3 (5.3)
Diabetic neuropathy	62 (23.6)	51 (24.8)	11 (19.3)
Diabetic nephropathy	34 (12.9)	26 (12.6)	8 (14.0)
Anti-diabetic therapies at baseline, n (%)			
Biguanides	206 (78.3)	157 (76.2)	49 (86.0)
Sodium-glucose co-transporter 2 inhibitors	159 (60.5)	122 (59.2)	37 (64.9)
Sulfonylureas	120 (45.6)	98 (47.6)	22 (38.6)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	92 (35.0)	83 (40.3)	9 (15.8)
Alpha glucosidase inhibitors	2 (0.8)	2 (1.0)	0
Thiazolidinediones	38 (14.4)	29 (14.1)	9 (15.8)
Combinations of OADs	34 (12.9)	28 (13.6)	6 (10.5)
Other blood glucose lowering drugs, excl. insulins	4 (1.5)	4 (1.9)	0

Data are mean (SD) unless otherwise specified.

BI, basal insulin; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide -1 receptor agonist; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; SD, standard deviation.

[a] Sum of responses exceeds 100% as more than one reason could be selected. [b] One patient reported a dose of 6.0 mg/day, which does not align with the recommended dose of liraglutide for patients with type 2 diabetes. This is likely due to a typing error (0.6 mg/day instead of 6.0 mg/day), but this was not possible to confirm as the site closed and contact was impeded. [c] In the 4 weeks prior to initiation of IDegLira treatment. [d] In the 26 weeks prior to initiation of IDegLira treatment.

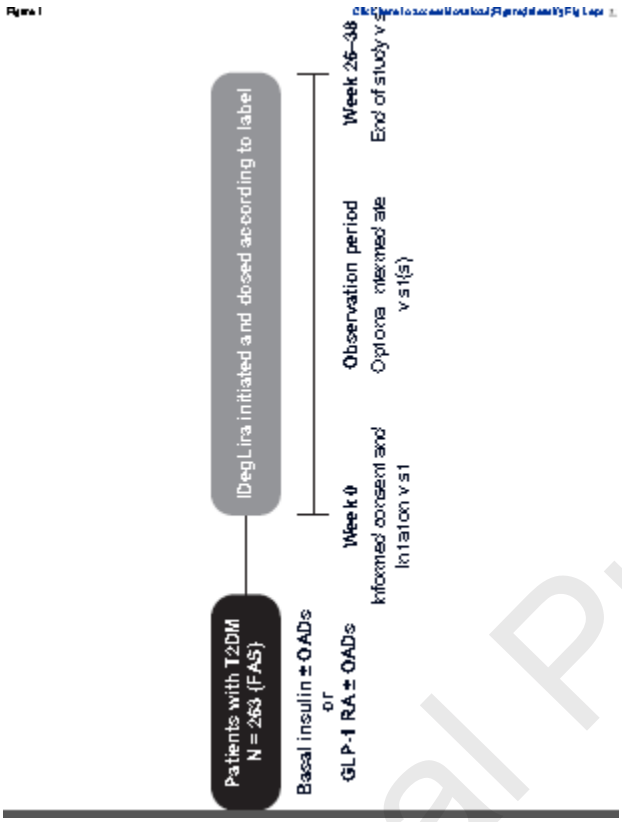
Table 2 Incidence of hypoglycaemic episodes.

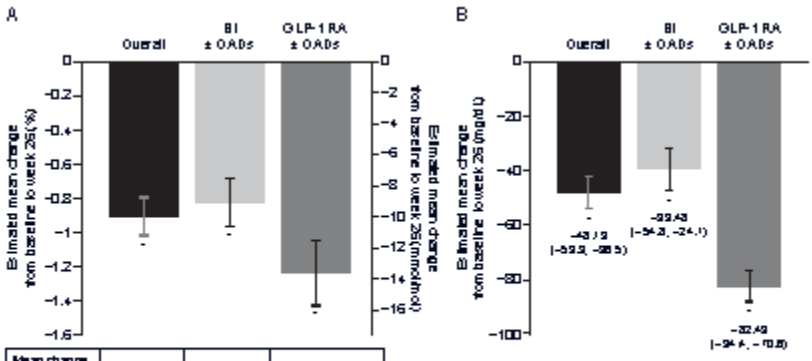
	Patients with events, N	Events, n	Estimate	Estimated incidence rate ratio (95% CI, p value)
Severe hypoglycaemic episodes (episodes/person year)				
Observed within 26 weeks prior to IDegLira initiation	3	4	0.0360	0.5008
Observed within 26 weeks prior to EOS/discontinuation	1	2	0.0224	(0.0, 10.0)
Estimated within 26 weeks prior to IDegLira initiation	3	4	0.0367	p = 0.6508
Estimated within 26 weeks prior to EOS/discontinuation	1	2	0.0184	
Non-severe hypoglycaemic episodes (episodes/person year)				
Observed within 4 weeks prior to IDegLira initiation	7	13	0.7405	0.1809
Observed within 4 weeks prior to EOS/discontinuation	1	2	0.1466	[0.0; 1.6]
Estimated within 4 weeks prior to IDegLira initiation	7	13	0.7435	p = 0.1281
Estimated within 4 weeks prior to EOS/discontinuation	1	2	0.1345	
Non-severe nocturnal hypoglycaemic episodes (episodes/person year)				
Observed within 4 weeks prior to IDegLira initiation	5	6	0.3418	0.3664
Observed within 4 weeks prior to EOS/discontinuation	1	2	0.1466	(0.0, 3.0)
Estimated within 4 weeks prior to IDegLira initiation	5	6	0.3506	p = 0.3495
Estimated within 4 weeks prior to EOS/discontinuation	1	2	0.1285	

CI, confidence interval; EOS, end of study.

[a] Based on adjusted negative binomial regression model specifying a log-transformed follow-up time offset term.

RESUBMISSION DRAFT





Mean change in HbA1c	Overall	BI ± OADs	GLP-1 RA ± OADs
% (95% CI)	−0.81 (−1.1, −0.5)	−0.69 (−1.0, −0.5)	−1.24 (−1.5, −0.9)
mmol/mol (95% CI)	−10.0 (−12.4, −7.5)	−9.0 (−11.3, −6.2)	−13.5 (−17.0, −9.1)

RESUBMISSION DRAFT