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IDegLira improves patient-reported outcomes while using a simple regimen with fewer injections and dose adjustments compared with basal–bolus therapy

Eden Miller DO[1] | Ankur Doshi MD[2] | Randi Grøn PhD[3] | Esteban Jódar MD[4] | Petra Őrsy MD[3] | Mattis F. Ranthe MD[3] | Danny Sugimoto MD[5] | Nikolaos Tentolouris MD[6] | Adie Viljoen MBChB[7] | Liana K. Billings MD[8,9]

[1]Diabetes Nation, Bend, Oregon

[2]PrimeCare Medical Group, Houston, Texas

[3]Novo Nordisk A/S, Søborg, Denmark

[4]University Hospital Quiron Salud, Madrid, Universidad Europea de Madrid, Madrid, Spain

[5]Cedar Crosse Research Center, Chicago, Illinois

[6]Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Medical School, Athens, Greece

[7]Borthwick Diabetes Research Centre, Lister Hospital, Stevenage, UK

[8]Internal Medicine, NorthShore University HealthSystem, Skokie, Illinois

[9]Internal Medicine, University of Chicago Pritzker School of Medicine, Chicago, Illinois

Correspondence
Eden Miller, DO, Diabetes Nation, 66965 Gist Rd, Bend, 97703 OR.
Email: kevineden@yahoo.com

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Abstract

Aims: Basal–bolus therapy is associated with greater treatment burden and lower adherence compared with more simplified regimens. This post hoc analysis studied the difference between insulin degludec/liraglutide (IDegLira) and basal–bolus therapy on number of injections, dose adjustments and patient outcomes in the DUAL VII trial.

Materials and methods: DUAL VII was a 26-week, open-label trial in which patients with uncontrolled type 2 diabetes who were using metformin and insulin glargine 100 units/mL (20–50 U) were randomized 1:1 to IDegLira (N = 252) or basal–bolus (insulin glargine U100 + insulin aspart ≤4 times/day) (N = 254). This post hoc analysis reports the observed mean number of injections and cumulative dose adjustments during 26 weeks of treatment. Patient-reported outcomes (Treatment-Related Impact Measure – Diabetes [TRIM-D] and Short Form-36 Health Survey version 2 [SF-36v2]) were collected at scheduled visits and change from baseline scores calculated.

Results: The clinical benefits (non-inferior HbA1c reductions, weight benefit, less hypoglycaemia) of IDegLira vs basal–bolus therapy were achieved with fewer cumulative dose adjustments (16.6 vs 217.2, respectively) and fewer injections (1 vs ≥3 per day, respectively). Patients treated with IDegLira experienced significant improvements across all TRIM-D domains compared with those undergoing basal–bolus therapy. The SF-36v2 showed improvements in both treatment arms with no significant difference between arms in the physical component summary, but there was a significant improvement in patients treated with IDegLira in the mental component summary (P = .0228).

Conclusions: These findings, combined with the DUAL VII results, suggest that IDegLira, through a more simplified regimen versus basal–bolus therapy, may help improve patient adherence and improve patient outcomes related to diabetes

management, treatment burden and mental health, which in turn may assist in the timely achievement of glycaemic control in clinical practice.

KEYWORDS
basal insulin, GLP-1RA analogue, type 2 diabetes

1 | INTRODUCTION

As a result of the chronic, progressive nature of type 2 diabetes (T2D), treatment intensification is often required to maintain glycaemic control. However, this is often delayed, a phenomenon referred to as clinical inertia.[1,2] One of the reasons for clinical inertia is the desire on the part of healthcare professionals (HCPs) and patients to avoid increasing treatment burden.[3] Studies have shown that increased treatment burden is associated with poorer adherence to treatment.[4-6] An improvement in adherence with fewer injections has been seen in a study in patients with T2D, which found that patients receiving basal insulin were more likely to persist with insulin therapy compared with patients on basal–bolus regimens (discontinuation rates of 28.7% compared with 35.4% after 12 months, excluding deaths, for basal insulin and basal–bolus therapy, respectively).[7] Poor adherence to treatment is a serious concern in clinical practice[5] as it has been associated with smaller reductions in glycated haemoglobin (HbA1c) levels,[8] increased emergency room visits and admissions, and longer hospital stays.[9,10] Insight into the patient's perspective on various treatment regimens can contribute to individualizing therapy and, potentially, to improving adherence.

The availability of glucagon-like peptide-1 receptor agonists (GLP-1RAs), injectable incretin mimetics that lower fasting and post-prandial blood glucose in a glucose-dependent manner, provides patients who have uncontrolled T2D with basal insulin an effective intensification option that offers a lower treatment burden, a reduced risk of hypoglycaemia, and weight loss or weight maintenance as opposed to weight gain, compared with intensifying therapy with prandial insulin.[11-13] Fixed ratio combination (FRC) injectable therapies with basal insulin/GLP1-RA therapy provide these advantages and further reduce treatment burden.[14-21]

Results from the DUAL clinical trial programme demonstrated that the FRC IDegLira combines the benefits of the basal insulin degludec (degludec) and the GLP-1RA, liraglutide, in a single daily injection, with a stepwise titration algorithm that contributes to attenuating the primary side effects associated with each component.[14-16,18-21] The DUAL VII trial compared the efficacy and safety of IDegLira with basal–bolus therapy (insulin glargine 100 units/mL [IGlar U100] + insulin aspart [IAsp] ≤4 times daily) in patients with T2D who were inadequately controlled with basal insulin and metformin.[20] IDegLira, administered as a once-daily injection, was non-inferior ($P < .0001$) to the multiple injections of basal–bolus therapy in reducing HbA1c from baseline (67 mmol/mol [8.2%]) to end of study (50 mmol/mol [6.7%]). Furthermore, treatment with IDegLira resulted in weight loss compared to the weight gain with basal–bolus therapy (−0.9 kg compared with +2.6 kg; $P < .0001$), and in fewer hypoglycaemic episodes (1.07 compared with 8.17 severe or blood glucose confirmed symptomatic hypoglycaemic episodes per patient year with IDegLira and basal–bolus, respectively; $P < .0001$).[20] Also of note, the cardiovascular safety of each component has been confirmed in their respective cardiovascular outcome trials.[22,23] Degludec demonstrated non-inferiority to IGlar U100[22] and liraglutide in reducing the risk of major adverse cardiovascular events compared with placebo.[23] Furthermore, post hoc sub-analyses of the DEVOTE[24] and DUAL programme[25] were in agreement with these findings, suggesting that cardiovascular safety was preserved.

The DUAL VII trial showed that IDegLira is as efficacious in reducing mean HbA1c as basal–bolus therapy, with fewer injections. In this study, we performed a post hoc analysis of the DUAL VII trial, which aimed to evaluate the extent to which the clinical benefits of IDegLira were achieved with a simpler dosing regimen in terms of number of injections and dose adjustments. Additionally, we looked at results from patient-reported outcome (PRO) questionnaires to assess the effect of each treatment on patients' self-perceived health status.

2 | MATERIALS AND METHODS

2.1 | Study design and interventions

The DUAL VII clinical trial programme (Clinical trial registration: NCT02420262) was an open-label, multinational, two-arm parallel, randomized trial in patients with T2D that was conducted at 89 sites in 12 countries from July 2015 to October 2016. Study design and methodology have been published previously (Figure 1).[20] Eligible patients were at least 18 years old with uncontrolled T2D (HbA1c, 53–86 mmol/mol [7.0%–10.0%]), with a BMI ≤40 kg/m^2, who were receiving stable daily doses of 20–50 units (U) of IGlar U100 and at least 1500 mg (or maximum tolerated dose) of metformin for more than 90 days prior to screening.[20] Patients were randomized to receive either 16 U of IDegLira (16 U insulin degludec +0.58 mg liraglutide) or to continue using basal IGlar U100 at the pre-trial dose (mean pre-trial insulin dose of 33 U) with the addition of IAsp four or fewer times daily. Metformin was continued at the pre-trial dose in both treatment arms (Figure 1).[20]

Both IDegLira and IGlar U100 were titrated twice weekly, using the same titration algorithm based on the mean of three consecutive pre-breakfast self-measured blood glucose (SMBG) values, to a target of 4.0–5.0 mmol/L (72–90 mg/dL). The bolus insulin component of basal–bolus therapy, IAsp, was initiated at 4 U/main meal and titrated twice weekly, to a pre-prandial and bedtime SMBG target of 4.0–6.0 mmol/L (72 to 108 mg/dL), using up to four boluses per day as required.

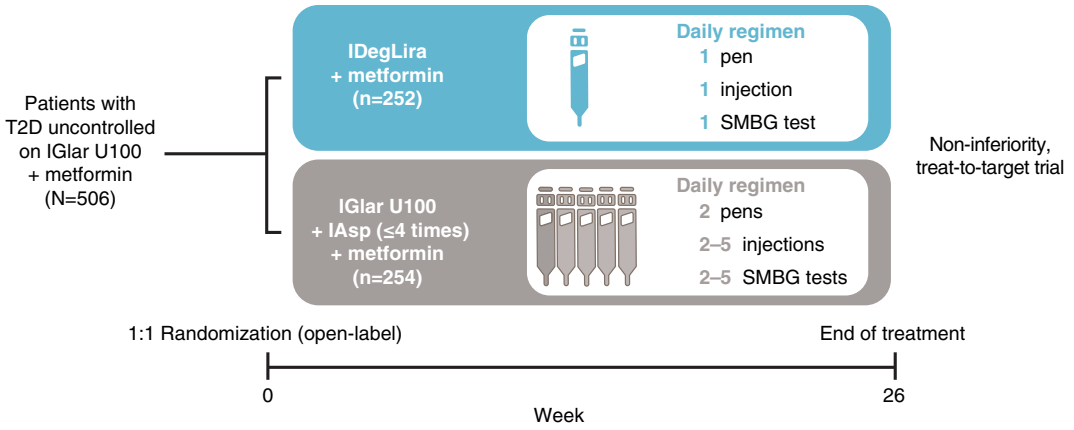


FIGURE 1 DUAL VII trial design. Number of injections and SMBG tests are based on number of meals. Abbreviations: FU, follow-up; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; SMBG, self-monitored plasma glucose; T2D, type 2 diabetes

The DUAL VII trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice[26] and the Declaration of Helsinki.[27]

2.2 | Patient-reported outcomes

PROs were collected at three scheduled visits (baseline, week 12 and week 26) and domain summary scores and change from baseline in summary scores were calculated. PRO questionnaires included the Treatment-Related Impact Measure for Diabetes (TRIM-D), comprising 28 items in five domains and a total score,[28,29] and the Short Form-36 Health Survey version 2 (SF-36 v2), consisting of 36 items in eight domains with two component summary scores.[30] TRIM-D scales (domain and total score) range from 0 to 100, with a higher score corresponding to a better outcome.[29] The minimally important difference (MID), defined as the smallest difference detected by patients, for TRIM-D has not been established. SF-36 scores were calculated using a 1998 reference population norm, in which a score of 50 corresponded to the norm for the adult general US population; higher scores corresponded with better outcomes.[30] The MID thresholds for SF-36 were taken from the user manual and ranged from 2 to 4; they were not specific to patients with diabetes.[31]

2.3 | Statistical analysis

Statistical analysis was based on a comparison between each treatment arm of the observed mean number of insulin injections and dose adjustments during 26 weeks of treatment, and of the number of patients receiving 0, 1, 2 or at least 3 bolus insulin injections at Week 26. Total and basal insulin dose and the number of insulin dose adjustments were based on the safety analysis set. Estimated treatment differences (ETDs) were based on the full analysis set. Change from baseline in PROs was analysed using a mixed-model for repeated measurements (MMRM), with treatment, region and visit as fixed factors and baseline value as covariate. Interactions between visit and all other factors and covariate were also assessed. Analysis of the PROs was not adjusted for multiplicity.

3 | RESULTS

The treatment arms were well matched with respect to baseline characteristics.[20] Of the 506 patients who were randomized to treatment, 94.4% (238/252) in the IDegLira arm and 91.7% (233/254) in the basal–bolus arm completed treatment.

3.1 | Regimen complexity

With IDegLira being initiated at 16 U and IGlar U100 being titrated from the pre-trial basal dose (mean 33 U)[20] (Figure 2), a similar number of adjustments in basal dose were observed for patients treated with IDegLira compared to those treated with IGlar U100 (16.6 compared with 17.1 adjustments, respectively, for the duration of the trial). Mean end-of-trial basal insulin dose was 40.4 U for IDegLira (40.4 U degludec and 1.5 mg liraglutide) and 52.3 U for IGlar U100. There were more dose adjustments for patients treated with IDegLira early in the trial compared with patients treated with IGlar U100. However, the number of dose adjustments in patients treated with IDegLira began to reduce at approximately Week 10, whereas reduction did not take place until Week 18 in patients treated with IGlar U100 (Figure 3A). Adjustments were made for patients in the IDegLira treatment group only in the basal dose (IDegLira), as there was no bolus component to this regimen. In the basal–bolus treatment arm, the mean number of cumulative bolus insulin adjustments required (considered regardless of meals, with the possibility of multiple daily adjustments) during the 26 weeks of treatment was 200 adjustments per patient (Figure 2). The number of bolus insulin dose adjustments over time increased at a faster rate, compared with basal insulin dose adjustments over time (Figure 3). Patients in the basal–bolus treatment group reached a total daily insulin dose of 84.1 U at Week 26 (52.3 U of basal IGlar 100 and 32.1 U of bolus IAsp).

At Week 26, approximately one-quarter (56/230; 24.3%) of patients in the basal–bolus treatment arm were receiving two bolus insulin injections and two-thirds (153/230; 66.5%) were receiving three or more bolus insulin injections daily (Figure 4). As these patients were also receiving a basal insulin injection, at Week 26 over 90% (209/230, 90.9%) of patients in this treatment arm were receiving three or more injections daily.

3.2 | Treatment-related impact measure – Diabetes

Improvements across all TRIM-D domains as well as in the total score were significantly greater ($P \leq .0268$) with IDegLira compared with basal–bolus treatment (Figure 5). Patients in the IDegLira treatment group showed moderate improvements across all TRIM-D domains and in the total score, while patients in the basal–bolus treatment group showed small improvements in the total score and across all domains, with the exception of daily life. The greatest differences between groups were in diabetes management (ETD: 10.76, $P < .0001$), treatment burden (ETD: 10.50, $P < .0001$) and compliance (ETD: 6.25, $P < .0001$). These domains include questions such as "How satisfied or dissatisfied have you been with the ease and convenience of your medication?" (treatment burden domain) and "How satisfied or dissatisfied

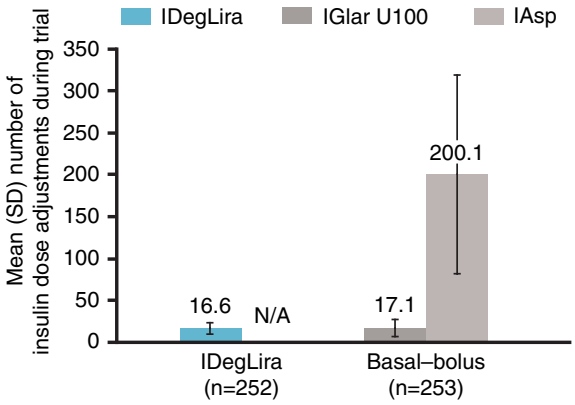


FIGURE 2 Mean cumulative number of insulin dose adjustments required during 26 weeks of treatment in the safety analysis set. Abbreviations: IDegLira, insulin degludec/liraglutide; SD, standard deviation

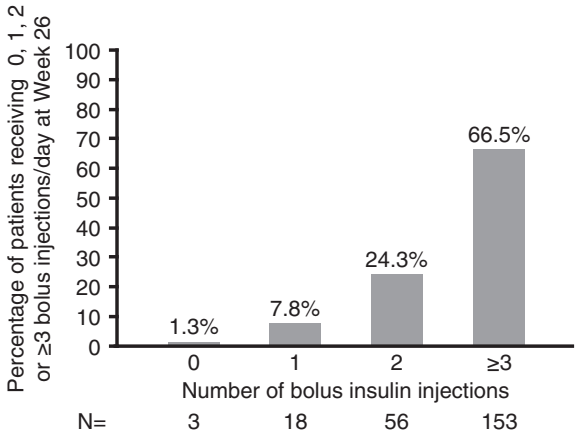


FIGURE 4 Percentage of patients receiving 0, 1, 2 or at least 3 bolus insulin injections per day in the basal–bolus treatment group at week 26 in the full analysis set. Abbreviations: IDegLira, insulin degludec/liraglutide

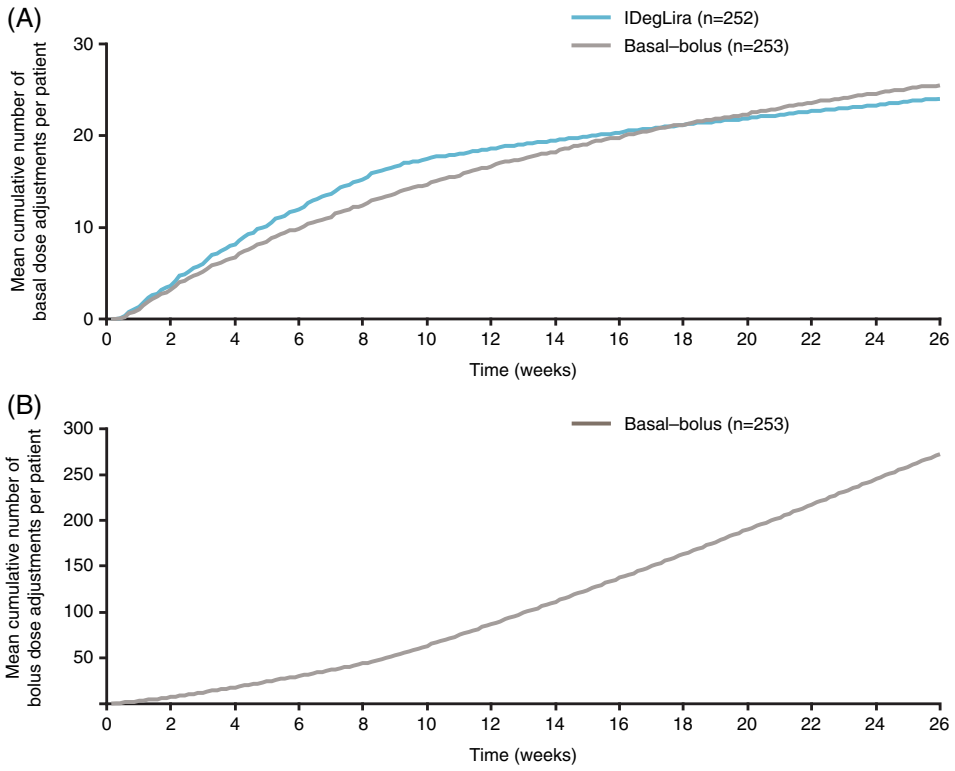
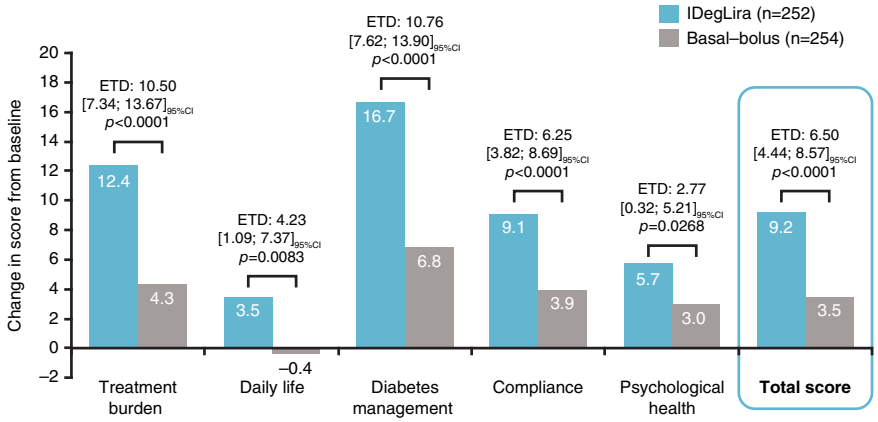


FIGURE 3 Mean cumulative number of (A) basal and (B) bolus insulin adjustments over time. Abbreviations: IDegLira, insulin degludec/liraglutide



	IDegLira	IGlar U100 + IAsp	IDegLira	IGlar U100 + IAsp	IDegLira	IGlar U100 + IAsp	IDegLira	IGlar U100 + IAsp	IDegLira	IGlar U100 + IAsp	IDegLira	IGlar U100 + IAsp
N at baseline	252	254	252	254	252	254	252	254	252	254	252	254
Score at baseline	66.0 (19.3)	61.3 (19.7)	79.1 (17.9)	77.5 (17.2)	55.8 (20.4)	54.3 (18.7)	81.0 (18.0)	79.3 (17.0)	80.8 (17.7)	80.0 (15.5)	72.9 (14.0)	70.9 (12.5)
N at Week 26	238	233	238	233	238	233	238	233	238	233	238	233
Score at Week 26	78.9 (17.8)	66.4 (21.4)	82.6 (18.1)	78.2 (19.7)	73.0 (17.9)	61.9 (20.0)	90.1 (12.5)	83.4 (16.5)	86.5 (13.8)	84.0 (16.8)	82.3 (12.0)	75.1 (14.4)

FIGURE 5 Change from baseline in TRIM-D domains and total score after 26 weeks of treatment. Mean (standard deviation) observed values based on full analysis set. Change from baseline after 26 weeks of treatment was analysed using an MMRM with an unstructured covariance matrix including treatment, visit and region as fixed factors and baseline response as covariate. Interactions between visit and all factors and covariates are also included in the model. Baseline data are means at Week 0. Abbreviations: CI, confidence interval; ETD, estimated treatment difference; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; MMRM, mixed model for repeated measurements; TRIM-D, Treatment-Related Impact Measure – Diabetes

are you with your medication's ability to help you avoid low blood sugar (hypoglycaemia)?" (diabetes management domain).

3.3 | Short Form-36 Health Survey version 2

Results of the SF-36 v2 showed improvements in both treatment arms in the physical component summary, but only in the IDegLira treatment arm in the mental component summary. Each treatment resulted in improvements across the individual domains, with the exception of the mental health domain in the basal–bolus arm. The ETD in change from baseline was statistically significantly greater with IDegLira compared with basal–bolus insulin in the mental component summary (P = .0228), in which greater improvements in each of the mental domains were observed with IDegLira but improvement was statistically significant only in the mental health domain (P = .0074) (Table S1). The improvement in the SF-36 v2 mental component observed in the IDegLira treatment group did not reach MID treatment thresholds (mental component summary ETD: 1.83, MID: 3; mental health domain ETD: 2.29, MID: 3).[31] No statistically significant differences between treatment arms were seen in the physical component summary or in any of the physical domains (Table S1). In addition, none of the differences in the physical component summary reached MID thresholds.

4 | DISCUSSION

This *post-hoc* analysis of the DUAL VII trial demonstrated that the previously reported clinical benefits of treatment with IDegLira over basal–bolus therapy,[20] such as greater percentage of patients reaching glycaemic targets without weight gain and/or hypoglycaemia, were achieved with fewer cumulative dose adjustments (16.6 compared with 217.2, respectively) and fewer injections (one compared with ≥ three per day, respectively). Furthermore, the hypothesis that fewer injections with less blood testing, fewer hypoglycaemic episodes and more weight loss would improve quality of life in patients treated with IDegLira as compared with basal–bolus therapy was substantiated with data from PROs.

While it is unlikely that insulin dose would be adjusted as frequently in clinical practice as is described here, it is evident that basal–bolus therapy necessitates more adjustments and, therefore, more dosing decisions than treatment with IDegLira. This is consistent with the primary DUAL VII results, which demonstrated that patients treated with IDegLira reached a stable insulin dose earlier and required a lower total daily insulin dose compared with patients in the basal–bolus treatment group, with similar reductions in HbA1c and improved clinical outcomes overall[20] without the added complexity. It is also worth noting that, in the DUAL VI trial,[19] a simpler once-weekly titration algorithm for IDegLira was compared with the twice-weekly algorithm used in all other DUAL trials in insulin-naïve patients; it was found that once-weekly titration of IDegLira, based on the average of two fasting blood glucose readings, resulted in a safety profile and a glycaemic efficacy profile similar to those with twice-weekly titration, based on the average of three fasting blood glucose readings.[19] This evidence suggests that IDegLira also has the potential to be as efficacious as basal–bolus

therapy in the real-world clinical setting, with fewer dose adjustments and fewer resources required to guide titration.

A greater number of dose adjustments and daily injections require more clinician support and more treatment decisions, which are often not feasible at the same level of rigour as in a clinical trial. With basal–bolus therapy, for example, each meal may require an SMBG reading before the meal, which, in turn, could necessitate a titration decision and an injection. There is thus a greater need for awareness on the part of patients concerning the way in which their diet impacts their insulin regimen. Unlike patients undergoing treatment with IDegLira, patients undergoing basal–bolus therapy must monitor the timing of meals and injections, as well as filling, storing and carrying prescriptions for different insulins. A basal–bolus insulin regimen, which requires patient awareness of insulin dose, meal size and physical activity, also confers a greater risk of hypoglycaemia than treatment with IDegLira[20] and may restrict lifestyle, or require precautions such as snacking, to prevent hypoglycaemic episodes. These decisions are likely to be even more complicated and require more support from HCPs when applied to a broad patient population that falls outside the inclusion/exclusion criteria of a clinical trial.

This analysis confirms the concept that a simpler injection regimen will result in improvements in PROs. The simpler dosing regimen offered by treatment with IDegLira compared with basal–bolus insulin therapy resulted in significantly greater improvements in disease-specific TRIM-D questionnaire scores of patients treated with IDegLira compared with those of patients undergoing basal–bolus insulin therapy. These improvements were greatest with IDegLira treatment as compared with basal–bolus insulin therapy in the domains of diabetes management, treatment burden and compliance. This is compatible with clinical findings as these PROs were based on questions such as satisfaction or dissatisfaction with ability to avoid hypoglycaemia, and ease and convenience of medication. These PRO data support the findings of Drummond et al.[32] from a European physicians' survey concerning real-world experience with IDegLira. Physicians reported decreased patient concern regarding weight gain and hypoglycaemia and greater satisfaction in terms of simplicity of therapy and number of injections with IDegLira treatment as compared with basal–bolus insulin therapy.[32] Improvements in PRO scores and outcomes may be indicative of patient adherence within clinical practice and have the potential to be increased with IDegLira treatment, as adherence to a treatment regimen is typically greater with simpler regimens.[33]

There was also a trend for improvements in the generic SF-36 v2 questionnaire domains and component summary scores; although the differences between IDegLira treatment and basal–bolus insulin therapy were statistically significant for the overall mental component summary and the mental health domain, these differences did not meet MID thresholds for clinical significance. While participants did not perceive any physical benefits with IDegLira treatment as compared with basal–bolus insulin therapy, the improvement in their overall mental component summary score indicated that patients felt more comfortable with IDegLira treatment, suggesting that the simpler dosing regimen with IDegLira is more reassuring to patients. There is also some evidence from animal studies to suggest that GLP-1RAs may have a positive effect on mood.[34] The greater improvements in PRO scores with IDegLira treatment are expected as IDegLira treatment provides a simpler regimen in terms of fewer daily injections, SMBG readings and dose adjustments, thus providing a lower treatment burden compared with basal–bolus insulin therapy and/or providing the clinical benefits of weight loss and low rates of hypoglycaemia.

A strength of this study is the novel approach to addressing and informing on the way in which two treatments that show similar reductions in HbA1c can impact the lifestyle of patients with a chronic disease by reducing treatment complexity. As the expectations for diabetes therapies move beyond improvements in HbA1c alone, these findings are pertinent for patients,[4,35] physicians,[3] payers[36] and regulators.[37,38] Another strength of this study is that the measurement of PROs uniquely obtains a patient's evaluation of treatment, which is not captured by clinical observation, physical examination or biochemical analysis, and understanding this aspect of patient care is just as important as clinical findings.

This study also has several limitations. The DUAL VII trial was open-label, which may have had an influence on study outcomes. However, blinding would have required additional placebo injections in the IDegLira arm and this would put unnecessary burden on patients and prevent an analysis of PROs. A second limitation is that the improvements in PRO scores, which were observed across all domains with IDegLira treatment and across the majority of domains with basal–bolus therapy, may be a clinical study effect, with participants in both treatment arms achieving good glycaemic control and receiving clinical support, which does not necessarily reflect real-world conditions. A third limitation is that the compliance domain scores should be interpreted with caution because of the subjective nature of the questions. For example, “How often do you delay or postpone taking your medication? never/almost never, rarely, sometimes, often or almost always/always?”. A further limitation of this study is that the analysis of PROs was not adjusted for multiplicity and, as a result, there is a potential for inflated type 1 error.

In conclusion, this *post-hoc* analysis demonstrates that treatment with IDegLira is a simple regimen, requiring fewer daily injections, fewer SMBG readings and fewer dose adjustments, and this is likely to be responsible, in part, for the observed improvement in the PROs of patients treated with IDegLira as compared with those receiving basal–bolus therapy. Taken together, these results and the improved clinical outcomes (non-inferior HbA1c, fewer episodes of hypoglycaemia and weight benefit) demonstrated with IDegLira treatment[20] suggest that it is less burdensome than basal–bolus therapy and has potential to improve patient adherence and compliance. In clinical practice, a treatment that requires fewer adjustments and measurements may facilitate timely achievement of glycaemic control.

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CONFLICT OF INTEREST

E. M. has participated in a speaker bureau and has served on advisory boards for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen and Novo Nordisk. M. F. R., R. G. and P. O. are employees of Novo Nordisk and own stocks in the company. N. T. has participated in advisory panels for Merck Sharp Dohme, AstraZeneca, Sanofi, Novo Nordisk, ELPEN, Eli Lilly, Servier, Boehringer Ingelheim and Novartis; and has received research support from Merck Sharp Dohme, Eli Lilly, Novo Nordisk, Sanofi, Pfizer, AstraZeneca, Janssen, Cilag, GlaxoSmithKline and Novartis. A. V. has served as advisor to and/or conducted research studies funded by and/or received lecture honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Napp, Novo Nordisk, Sanofi Aventis. E. J. has participated in advisory panels for Amgen, AstraZeneca, FAES, Eli Lilly, Merck Sharp Dohme and Novo Nordisk; and has received research funding from Amgen, Boehringer, AstraZeneca, GlaxoSmithKline, FAES, Janssen, Eli Lilly, Merck Sharp Dohme, Novo Nordisk, Pfizer and Sanofi, and participates in a speaker bureau for Amgen, AstraZeneca, Boehringer, FAES, Eli Lilly, Merck Sharp Dohme, Novartis and Novo Nordisk. L. K. B. has participated in advisory panels for Novo Nordisk and Sanofi; has received speaking fees from Novo Nordisk; and has received research support from Novo Nordisk, Sanofi, Eli Lilly and Dexcom.

AUTHOR CONTRIBUTIONS

All authors confirm that they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have contributed to: collection of data, critical analysis and interpretation of the data, drafting/critically revising the article and sharing in the final responsibility for the content of the manuscript and the decision to submit it for publication. E. M. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data.

DATA ACCESSIBILITY STATEMENT

The subject level analysis data sets for the research presented in the publication are available from the corresponding author upon reasonable request.

ORCID

Eden Miller https://orcid.org/0000-0001-8733-8802
Danny Sugimoto https://orcid.org/0000-0002-7801-1231

REFERENCES

1. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. *Diabetes Obes Metab*. 2016;18:401-409.
2. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80 000 people. *Diabetes Care*. 2013;36:3411-3417.
3. Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. *Diabetes Obes Metab*. 2018;20:488-496.
4. Brod M, Pfeiffer KM, Barnett AH, Berntorp K, Vilsboll T, Weissenberger B. Perceptions of diabetes control among physicians and people with type 2 diabetes uncontrolled on basal insulin in Sweden, Switzerland, and the United Kingdom. *Curr Med Res Opin*. 2016;32:981-989.
5. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. *Diabetes Care*. 2010;33:240-245.
6. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care*. 2009;15:e22-e33.
7. Roussel R, Charbonnel B, Behar M, Gourmelen J, Emery C, Detournay B. Persistence with insulin therapy in patients with type 2 diabetes in France: an insurance claims study. *Diabetes Ther*. 2016;7:537-549.
8. Farmer AJ, Rodgers LR, Lonergan M, et al. Adherence to oral glucose-lowering therapies and associations with 1-year HbA1c: a retrospective cohort analysis in a large primary care database. *Diabetes Care*. 2016;39:258-263.
9. Boye KS, Curtis SE, Lage MJ, Garcia-Perez LE. Associations between adherence and outcomes among older, type 2 diabetes patients: evidence from a Medicare supplemental database. *Patient Prefer Adherence*. 2016;10:1573-1581.
10. Jha AK, Aubert RE, Yao J, Teagarden JR, Epstein RS. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly $5 billion annually. *Health Aff*. 2012;31:1836-1846.
11. Berlie H, Hurren KM, Pinelli NR. Glucagon-like peptide-1 receptor agonists as add-on therapy to basal insulin in patients with type 2 diabetes: a systematic review. *Diabetes Metab Syndr Obes*. 2012;5:165-174.
12. 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;10:26.
13. Vora J, Bain SC, Damci T, et al. Incretin-based therapy in combination with basal insulin: a promising tactic for the treatment of type 2 diabetes. *Diabetes Metab*. 2013;39:6-15.
14. Gough SC, Bode B, Woo V, 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;2:885-893.
15. Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). *Diabetes Care*. 2014;37:2926-2933.
16. Linjawi S, Bode BW, Chaykin LB, 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;8:101-114.
17. Rodbard HW, Bode BW, Harris SB, et al. the Dual Action of Liraglutide and insulin degludec (DUAL) IV Trial Investigators. 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;34:189-196.
18. Lingvay I, Pérez Manghi F, Garcia-Hernandez P, 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;315:898-907.
19. Harris SB, Kocsis G, Prager R, 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;19:858-865.
20. Billings LK, Doshi A, Gouet D, 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;41:1009-1016.
21. Philis-Tsimikas A, Billings LK, Busch R, 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 patients with uncontrolled type 2 diabetes. *Diabetes Obes Metab*. 2019;21:1399-1408. [Epub ahead of print].
22. Marso SP, McGuire DK, Zinman B, et al. DEVOTE Study Group. Efficacy and safety of Degludec versus Glargine in type 2 diabetes. *N Engl J Med*. 2017;377:723-732.
23. Marso SP, Daniels GH, Brown-Frandsen K, et al. LEADER Steering Committee, LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.
24. Brown-Frandsen K, Emerson SS, McGuire DK, et al. Lower rates of cardiovascular events and mortality associated with liraglutide use in patients treated with basal insulin – a DEVOTE subanalysis (DEVOTE 10). *Diabetes Obes Metab*. 2019;21:1437-1444. [Epub ahead of print].
25. Vilsboll T, Blevins TC, Jodar E, et al. Fixed-ratio combination of insulin degludec and liraglutide (IDegLira) improves cardiovascular risk markers in patients with type 2 diabetes uncontrolled on basal insulin. *Diabetes Obes Metab*. 2019;21:1506-1512. [Epub ahead of print].
26. International Conference of Harmonisation. *ICH Harmonised Tripartite Guideline. Good Clinical Practice*. 1996. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Accessed July 29, 2019.
27. World Medical Association. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194.
28. Brod M, Christensen T, Hammer M, Busk AK, Bushnell DM. Examining the ability to detect change using the TRIM-diabetes and TRIM-diabetes device measures. *Qual Life Res*. 2011;20:1513-1518.
29. Brod M, Hammer M, Christensen T, Lessard S, Bushnell DM. Understanding and assessing the impact of treatment in diabetes: the treatment-related impact measures for diabetes and devices (TRIM-diabetes and TRIM-diabetes device). *Health Qual Life Outcomes*. 2009;7:83.
30. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*. 1992;30(6):473-483.
31. Maruish ME. *User's Manual for the SF-36v2 Health Survey*. 3rd ed. Lincoln, RI: QualityMetric, Inc; 2011.
32. 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:e000531.
33. Barbosa CD, Balp M-M, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. *Patient Prefer Adherence*. 2012;6:39-48.
34. Anderberg RH, Richard JE, Hansson C, Nissbrandt H, Bergquist F, Skibicka KP. GLP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. *Psychoneuroendocrinology*. 2016;65:54-66.
35. Hixson-Wallace JA, Dotson JB, Blakey SA. Effect of regimen complexity on patient satisfaction and compliance with warfarin therapy. *Clin Appl Thromb Hemost*. 2001;7:33-37.
36. Davies MJ, D'Alessio DA, Fradkin J, 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;41:2669-2701.
37. Beyond A1C Writing Group. Need for regulatory change to incorporate beyond A1C glycemic metrics. *Diabetes Care*. 2018;41:e92-e94.
38. US Food and Drug Administration. Public Workshop: diabetes outcome measures beyond hemoglobin A1c (HbA1c). 2016. https://www.fda.gov/drugs/newsevents/ucm499281.htm. Accessed July 29, 2019.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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