BRIEF REPORT

WILEY

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

Giorgio Sesti MD[1] | Lars Bardtrum MS[2] | Selcuk Dagdelen MD[3] |
Natalie Halladin PhD[2] | Martin Haluzík PhD[4] | Petra Őrsy MD[2] |
Martin Rodríguez MD[5] | Vanita R. Aroda MD[6,7]

[1] Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

[2] Novo Nordisk A/S, Søborg, Denmark

[3] Department of Endocrinology and Metabolism, Hacettepe University School of Medicine, Ankara, Turkey

[4] Institute for Clinical and Experimental Medicine and Institute of Endocrinology, Prague, Czech Republic

[5] Area of Endocrinology, Metabolism and Nutrition, Faculty of Medical Sciences, National University of Cuyo, Mendoza, Argentina

[6] Brigham and Women's Hospital, Boston, Massachusetts, United States

[7] MedStar Health Research Institute, Hyattsville, Maryland, United States

Correspondence
Giorgio Sesti, Department of Clinical and Molecular Medicine, Sapienza University of Rome, Via di Grottarossa 1035-1039, 00189, Rome, Italy.
Email: giorgio.sesti@uniroma1.it

Abstract

This report presents the efficacy and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine 100 units/mL (IGlar U100) as initial injectable therapy at 26 weeks in the 104-week DUAL VIII durability trial (NCT02501161). Participants (N = 1012) with type 2 diabetes (T2D) uncontrolled on oral antidiabetic drugs (OADs) were randomized 1:1 to open-label IDegLira or IGlar U100. Visits were scheduled at weeks 1, 2, 4 and 12, and every 3 months thereafter. After 26 weeks, glycated haemoglobin (HbA1c) reductions were greater with IDegLira versus IGlar U100 (−21.5 vs. −16.4 mmol/mol [−2.0 vs. −1.5%]), as was the percentage of participants achieving HbA1c <53 mmol/mol (78.7% vs. 55.7%) and HbA1c targets without weight gain and/or hypoglycaemia. Estimated treatment differences for insulin dose (−13.01 U) and body weight change (−1.57 kg) significantly favoured IDegLira. The hypoglycaemia rate was 44% lower with IDegLira versus IGlar U100. Safety results were similar. In a trial resembling clinical practice, more participants receiving IDegLira than IGlar U100 met treatment targets, supporting use of IDegLira as an initial injectable therapy for people with T2D uncontrolled on OADs and eligible for insulin initiation.

KEYWORDS
clinical trial, insulin degludec, liraglutide, type 2 diabetes

1 | INTRODUCTION

Because of its progressive nature, people with type 2 diabetes (T2D) often eventually require injectable therapies to achieve glycaemic control. The current guidelines for management of T2D recommend injectable therapies when oral antidiabetic drugs (OADs) have failed to achieve control, with glucagon-like peptide-1 receptor agonists (GLP-1RAs) now being the recommended first choice of injectable

drug in most cases.[1,2] Although GLP-1RAs are recommended, basal insulin currently remains the most widely used first injectable therapy,[3-5] particularly in people with high glycated haemoglobin (HbA1c) levels.[1,2] A fixed-ratio combination therapy of basal insulin and GLP-1RAs, such as insulin degludec/liraglutide (IDegLira), is a possible alternative treatment choice for an initial injectable therapy, based on evidence from the DUAL clinical development programme.[6-10]

In the 104-week DUAL VIII trial, which had a schedule designed to resemble recommended clinical practice, treatment with IDegLira resulted in a significantly longer time before treatment intensification was needed compared with insulin glargine 100 units/mL (IGlar U100; median duration >2 years with IDegLira and ~1 year for IGlar U100).[11] The first 26 weeks of this trial were aimed at optimizing titration of the randomized injectable, with the goal of reaching HbA1c <53 mmol/mol (<7.0%). Throughout DUAL VIII, clinic visits were scheduled less frequently than typical treat-to-target diabetes trials, and titration was guided entirely by the investigator, with no external monitoring beyond trial site staff.

We report the prespecified efficacy and safety outcomes at week 26 to assess whether previously seen efficacy benefits of initiating IDegLira compared with IGlar U100 were observed in the initial titration and dose optimization within the first 26 weeks, in a trial with a visit frequency resembling recommended clinical practice in a population of participants with T2D inadequately controlled with OADs.

2 | MATERIALS AND METHODS

2.1 | Trial design

DUAL VIII was a phase 3b, multinational, open-label, two-arm parallel, 104-week randomized trial (NCT02501161) consisting of a 2-week screening period, a 104-week treatment period and two follow-up safety assessments (Figure S1). Three clinic visits (weeks 2, 4 and 12) and one telephone contact were scheduled between baseline and week 12, to guide insulin-naïve participants on how to titrate the trial drug, with visits every 3 months thereafter, to assess the need for treatment intensification, thereby mirroring recommendations in the current guidelines for management of T2D.[1,2] Unscheduled visits were performed if required, specifically if an adverse event (AE) needed further attention or additional laboratory samples/testing were needed.

DUAL VIII was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki.[12,13] Informed consent was obtained before any trial-related activities.

2.2 | Participants

Inclusion and exclusion criteria have been published previously.[11]

2.3 | Procedures/interventions

Participants were randomized 1:1 to receive either IDegLira in a 3-mL prefilled PDS290 pen or IGlar U100 in a 3-mL prefilled Solostar® pen, both administered once daily by subcutaneous injection, in combination with OAD(s) using an interactive web response system.

Both treatments, IDegLira (1 U = 1 U degludec + 0.036 mg liraglutide) and IGlar U100, were initiated at 10 U. The maximum dose of IDegLira was 50 U and there was no maximum dose for IGlar U100. Investigators were guided to titrate twice weekly to a fasting plasma glucose (FPG) target of 4.0 to 5.0 mmol/L (72–90 mg/dL); adjustments were made in increments of 2 U. Full details of the titration of IDegLira and IGlar U100 can be found in the Supporting Information (Table S1).

2.4 | Prespecified outcome measures

The present report details safety and efficacy data up to week 26 only; endpoints derived from the entire 104-week treatment period have been reported previously.[11] Supportive secondary efficacy endpoints included change from baseline in HbA1c and body weight after 26 weeks of treatment, daily insulin dose at week 26, proportion of participants achieving HbA1c targets of <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%), and the composite endpoint of HbA1c targets without hypoglycaemia and/or without weight gain by week 26. For the composite endpoints, it was prespecified that only hypoglycaemic events during the last 12 weeks of treatment leading up to week 26 would be assessed, in keeping with previous DUAL trials. Safety endpoints included the number of treatment-emergent severe (requiring third-party assistance) or blood glucose-confirmed (<3.1 mmol/L [<56 mg/dL]) symptomatic hypoglycaemic events during 26 weeks of treatment, and the number of treatment-emergent AEs during 26 weeks of treatment.

2.5 | Statistical analyses

Full statistical analysis details can be found in the Supporting Information.

3 | RESULTS

In total, 506 participants were randomized to each treatment arm and 506/504 participants received at least one dose of IDegLira/IGlar U100, respectively. Baseline characteristics were well matched.[11]

3.1 | Key efficacy and safety endpoints

3.1.1 | Glycaemic control

Mean change from baseline (least squares [LS] mean) in HbA1c was −21.5 mmol/mol (−2.0%) with IDegLira and −16.4 mmol/mol (−1.5%) with IGlar U100 after 26 weeks of treatment, corresponding to an
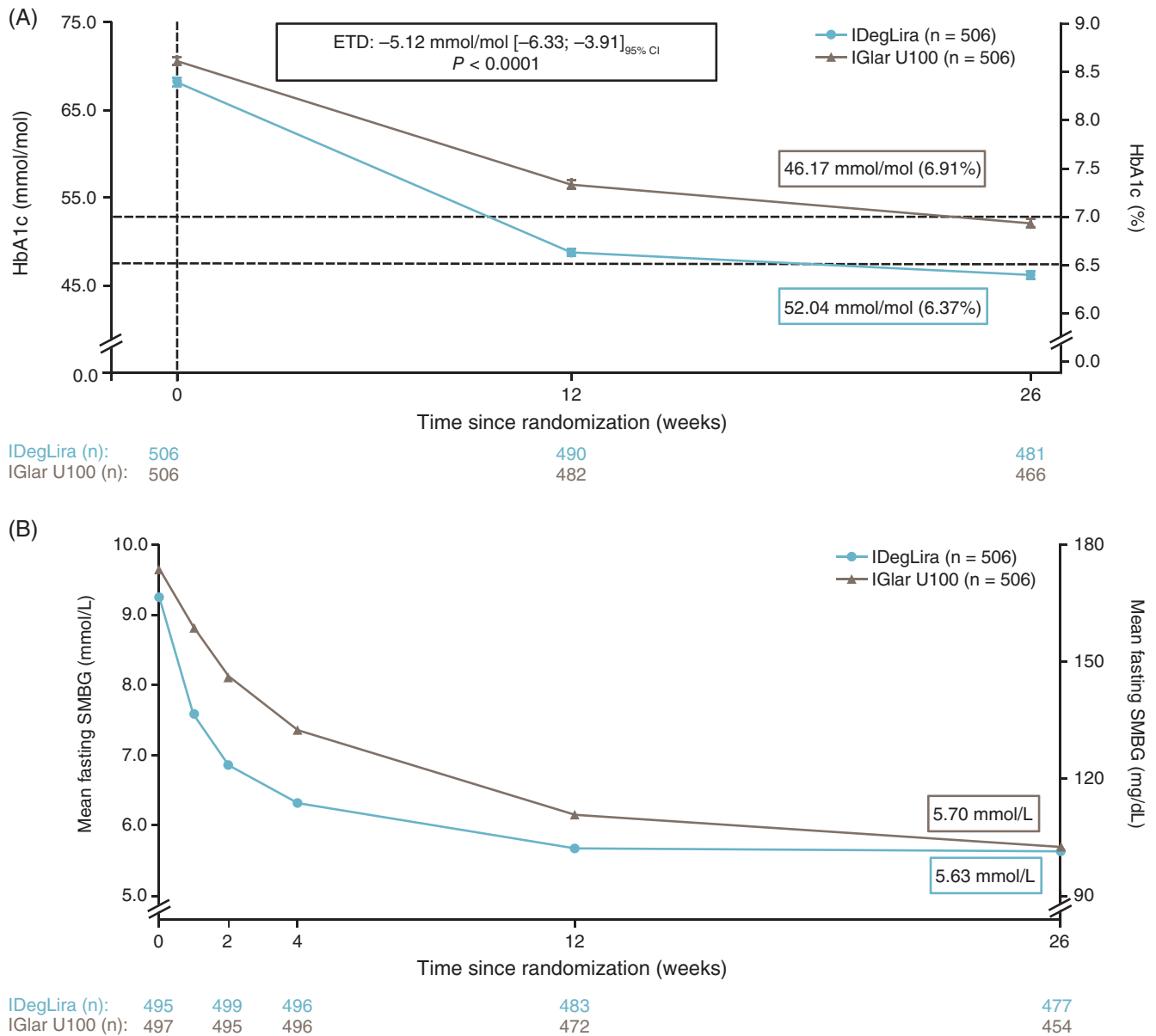
FIGURE 1 Glycaemic control. A) Glycated haemoglobin (HbA1c) concentration over time and B) self-measured blood glucose (SMBG) for dose adjustment. Data are observed means based on the full analysis set. Numbers of participants contributing to the data points appear in the bottom panel. CI, confidence interval; ETD, estimated treatment difference; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL

estimated treatment difference (ETD) of −5.12 mmol/mol (95% confidence interval [CI] −6.33 to −3.91; −0.47% [95% CI −0.58 to −0.36]; P < 0.0001 [Figure 1]).

3.1.2 | Other key efficacy endpoints

A greater proportion of participants treated with IDegLira versus IGlar U100 achieved the composite endpoints of HbA1c <53 mmol/mol (<7.0%) without hypoglycaemia (71.3 vs. 44.9%), HbA1c <53 mmol/mol (<7.0%) without weight gain (38.5 vs. 15.4%) and HbA1c <53 mmol/mol (<7.0%) without hypoglycaemia and weight gain (35.2

vs. 13.6%). The odds of participants achieving HbA1c targets of <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%) were significantly greater with IDegLira compared with IGlar U100, as were the odds of achieving the composite endpoints of HbA1c targets without weight gain and/or hypoglycaemia, after 26 weeks of treatment (Figure 2). Mean change from baseline (LS mean) in body weight was 0.5 kg with IDegLira and 2.1 kg with IGlar U100 (ETD −1.57 kg [95% CI −2.00 to −1.13]; P < 0.0001 [Figure S2]). Mean daily insulin dose (LS mean) at week 26 was lower with IDegLira (35.4 U) compared with IGlar U100 (48.4 U; ETD −13.01 U [95% CI −15.03 to −10.99]; P <0.0001).

Over 26 weeks, the rate of severe or blood glucose-confirmed symptomatic hypoglycaemia was significantly lower with IDegLira
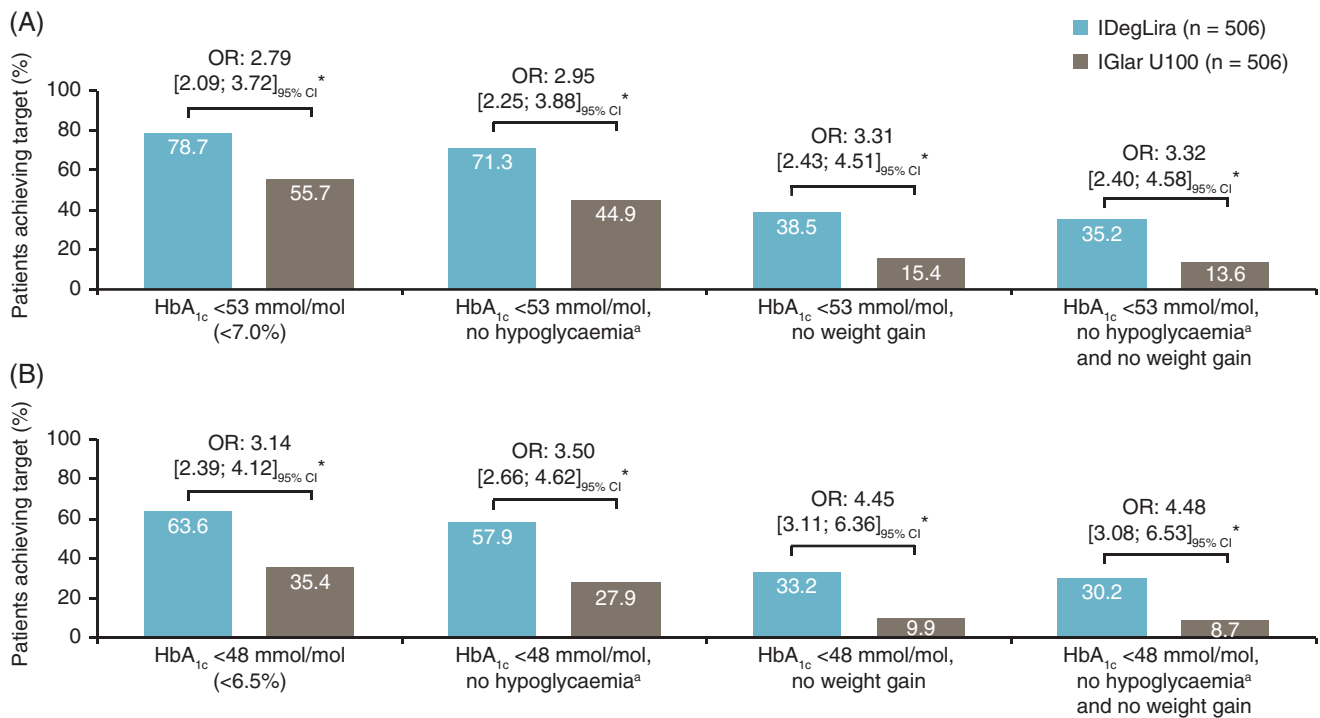
FIGURE 2 Attainment of treatment targets with insulin degludec/liraglutide (IDegLira) versus insulin glargine 100 units/mL (IGlar U100). %, based on observed data. Odds ratios (ORs; IDegLira/IGlar U100) are from a logistic regression model with treatment, baseline glycated haemoglobin (HbA1c) group, pre-trial OAD and region as factors and baseline HbA1c (and body weight for endpoints including "without weight gain") as a covariate. *Statistically significant difference (in favour of IDegLira). [a]Severe or blood glucose-confirmed (<3.1 mmol/L) symptomatic hypoglycaemia was based on hypoglycaemic episodes during a participant's last 12 weeks of treatment. CI, confidence interval; OAD, oral antidiabetic drug

versus IGlar U100 (LS mean 53.7 vs. 95.3 events/100 participant-years of exposure [PYE], rate ratio 0.56 [95% CI 0.39 to 0.82]; P = 0.0023). The mean cumulative number of severe or blood glucose-confirmed symptomatic hypoglycaemic events over time is shown in Figure S3. Rates of nocturnal severe or blood glucose-confirmed symptomatic hypoglycaemia (occurring between 12:01 and 5:59 AM [both inclusive]) were also significantly lower with IDegLira versus IGlar U100 (LS mean 8.8 vs. 19.5 events/100 PYE, rate ratio 0.45 [95% CI 0.24 to 0.83]; P = 0.0102).

3.1.3 | Adverse events

Rates of AEs were 291.0 events/100 PYE with IDegLira and 257.5 events/100 PYE with IGlar U100. The majority of AEs were non-serious, mild in severity and unlikely to be related to trial products, as judged by the investigator. Two fatal events occurred during the first 26 weeks; both were in the IGlar U100 treatment arm and considered unlikely to be related to trial product.

4 | DISCUSSION

The present analysis of the DUAL VIII trial demonstrated that, after the initial 26 weeks, more participants achieved clinically relevant

composite endpoints (HbA1c targets without weight gain and/or hypoglycaemia) with IDegLira than with IGlar U100.

During the DUAL VIII trial, titration was guided entirely by the investigator, with no external monitoring beyond trial site staff, with one scheduled telephone contact and visits at weeks 1, 2, 4 and 12, and every 3 months thereafter, mirroring recommendations in the current guidelines for management of T2D.[1,2,11]

Attainment of treatment targets at week 26 in the DUAL VIII trial was consistent with previous DUAL trials. In trials conducted in post-OAD populations, more IDegLira-treated participants achieved HbA1c <53 mmol/mol (<7.0%) without weight gain and without hypoglycaemia compared with degludec alone or IGlar U100.[6,7] These trials illustrate the advantages of a combination of liraglutide and degludec over basal insulin alone. The improved efficacy probably reflects the complementary action of the two components, with degludec reducing FPG and HbA1c, and liraglutide reducing both FPG and postprandial glucose control in a glucose-dependent manner. In addition, the mechanism of action of liraglutide addresses multiple aspects of the underlying pathogenic abnormalities in T2D (eg, declining β-cell function, excessive secretion of glucagon from pancreatic α cells, lipotoxicity, and insulin resistance in liver and peripheral tissues) and has been shown to lower the risk of cardiovascular disease and mortality in individuals at increased risk.[14,15] The beneficial effects with respect to weight and hypoglycaemia with IDegLira versus basal insulin are likely to predominantly be a result of the lower insulin

requirement made possible by the liraglutide component, but may also be partly attributable to the reduced rates of hypoglycaemia reported for degludec versus IGlar U100.[16-18]

Our results are consistent with the demonstrated insulin-sparing effects of IDegLira compared with IGlar U100.[7] End-of-trial insulin dose was also significantly lower with IDegLira versus degludec in insulin-naïve participants during the 26-week treatment in DUAL I (wherein IDegLira demonstrated non-inferiority to degludec for change in HbA1c). The DUAL I trial represented a typical treat-to-target diabetes trial, with guidance on titration given during 18 telephone contacts and 11 scheduled site visits, with any significant deviations from the titration algorithm being addressed by an external titration committee.[6] That insulin doses at week 26 were only slightly lower (IDegLira: 35 U; IGlar U100: 48 U) than in DUAL I (IDegLira: 38 U; degludec: 53 U) suggests that, while still under clinical trial conditions, the lower frequency of clinic visits is sufficient to guide appropriate titration.[6] However, comparisons should be made cautiously, as the participants in DUAL VIII received more OADs and had a longer duration of diabetes compared with participants in DUAL I.[6]

The results also build on the available safety data for IDegLira, with no unexpected safety findings and low overall rates of AEs.[9] Full safety results of the 104-week trial have been reported previously.[11]

The present trial did not include a treatment arm randomizing participants to receive GLP-1RA therapy alone, which would be an alternative initial injectable therapy for people uncontrolled on OADs. Basal insulin was chosen as a comparator as it is the most widely used injectable antidiabetic therapy. The major strength of this study was that the trial design mirrored clinical practice, with investigator-guided titration. With this design we still showed attainment of treatment targets without the visit frequency and strict titration protocol of typical treat-to-target trials, in a trial population that reflects people with T2D eligible for basal insulin initiation.

In conclusion, after 26 weeks of treatment in a trial design resembling recommended clinical practice, more participants met treatment targets with IDegLira versus IGlar U100, with a lower insulin dose and with less hypoglycaemia and weight gain, which supports the use of IDegLira as a first injectable therapy for people with T2D eligible for treatment intensification.

ACKNOWLEDGMENTS

CONFLICTS OF INTEREST

G.S. has received speaker/consulting honoraria from Novo Nordisk, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Sanofi, Amgen, Abbott, GlaxoSmithKline and Servier. L.B., N.H. and P.Ő. are employees and shareholders at Novo Nordisk A/S. S.D. has been involved in international randomized clinical trials with Novo Nordisk, Sanofi, Takeda, Astra Zeneca and advisory boards for Novo Nordisk, Sanofi, Astra Zeneca, Bristol Myers Squib, Boehringer İngelheim, Merck

Sharp & Dohme, Novartis and Servier. M.H. has been involved in various advisory boards for Novo Nordisk, speaker panel and multinational trials with Novo Nordisk products. M.R. has served as an advisory board member for Novo Nordisk, GlaxoSmithKline, Sanofi, Eli Lilly, Bristol Myers Squib, Janssen Cilag, Boehringer Ingelheim and Astra Zeneca, a speaker at meetings organized by Eli Lilly, Novo Nordisk, Bristol Myers Squib, Astra Zeneca, Merck, Sharp & Dohme, GlaxoSmithKline, Craveri, Sanofi, Novartis and Boehringer Ingelheim, and principal investigator of trials for Eli Lilly, Novo Nordisk, Novartis, Icon, Bristol Myers Squib and Boehringer Ingelheim. V.A. has served as a consultant for Adocia, Astra Zeneca, BD, Novo Nordisk, Sanofi, Zafgen, her spouse is employed at Merck Research Laboratories, and she has received research support (to institution) from Astra Zeneca/BMS, Calibra, Eisai, Janssen, Novo Nordisk, Sanofi and Theracos.

AUTHOR CONTRIBUTIONS

All authors had full access to all data, were responsible for data interpretation and manuscript preparation and had final responsibility for the decision to submit for publication.

DATA ACCESSIBILITY STATEMENT

The patient-level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

FUNDING INFORMATION

ORCID

Giorgio Sesti https://orcid.org/0000-0002-1618-7688
Martin Haluzík https://orcid.org/0000-0002-0201-6888
Vanita R. Aroda https://orcid.org/0000-0002-7706-4585

REFERENCES

1. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S90-S102.
2. 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.
3. Roumie CL, Greevy RA, Grijalva CG, Hung AM, Liu X, Griffin MR. Diabetes treatment intensification and associated changes in HbA1c and body mass index: a cohort study. *BMC Endocr Disord*. 2016;16:32.
4. Blonde L, Raccah D, Lew E, et al. Treatment intensification in type 2 diabetes: A real-world study of 2-OAD regimens, GLP-1 RAs, or basal insulin. *Diabetes Ther*. 2018;9:1169-1184.
5. Buysman EK, Fan T, Blauer-Peterson C, Miller-Wilson LA. Glycaemic impact of treatment intensification in patients with type 2 diabetes uncontrolled with oral antidiabetes drugs or basal insulin. *Endocrinol Diabetes Metab*. 2018;1:e00019.
6. 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.

7. 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 people with uncontrolled type 2 diabetes. *Diabetes Obes Metab*. 2019;21:1399-1408.

8. Rodbard HW, Bode BW, Harris SB, 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: 189-196.

9. Gough SC, Bode BW, Woo VC, et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. *Diabetes Obes Metab*. 2015;17:965-973.

10. 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.

11. Aroda VR, Gonzalez-Galvez G, Gron R, et al. Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:596-605.

12. International Conference of Harmonisation. ICH Harmonised Tripartite Guideline. *Good Clinical Practice*; 1996.

13. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194.

14. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375: 311-322.

15. Abdul-Ghani M, DeFronzo RA. Is it time to change the type 2 diabetes treatment paradigm? Yes! GLP-1 RAs should replace metformin in the type 2 diabetes algorithm. *Diabetes Care*. 2017;40:1121-1127.

16. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab*. 2013;15:175-184.

17. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obes Metab*. 2012;14:859-864.

18. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med*. 2017;377: 723-732.

SUPPORTING INFORMATION

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