Evaluation of the Short-Term Cost-Effectiveness of IDegLira Versus Basal Insulin and Basal-Bolus Therapy in Patients with Type 2 Diabetes Based on Attainment of Clinically Relevant Treatment Targets

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ABSTRACT

BACKGROUND: Effective glycemic control can reduce the risk of complications and their related costs in patients with type 2 diabetes (T2D). Many patients fail to reach hemoglobin A1c (HbA1c) $\leq 6.5\%$ or $< 7.0\%$, often due to adverse effects of treatment, such as hypoglycemia and weight gain. Glycemic targets should be individualized and consider multiple factors, including the risk of adverse events and the patient's characteristics and comorbid conditions.

OBJECTIVE: To compare the odds and annual cost of achieving treatment targets, which incorporate HbA1c targets of $< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$, with insulin degludec/liraglutide (IDegLira) versus basal insulin and basal-bolus therapy.

METHODS: This is a post hoc analysis of the DUAL V and DUAL VII 26-week trials, which randomized patients with T2D uncontrolled (HbA1c 7%-10%) on insulin glargine 100 units/mL (IGlar U100) and metformin to IDegLira or continued IGlar U100 titration (DUAL V) or IGlar U100 + insulin aspart (DUAL VII), all with metformin. Proportions of patients achieving HbA1c targets ($< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$) by the end of trial were assessed via 3 outcomes: alone, without either hypoglycemia or weight gain (double composite outcome), or without a combination of hypoglycemia and weight gain (triple composite outcome). The cost per patient achieving the triple composite outcome at each HbA1c target ($< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$) was calculated by dividing the annual cost of treatment by the proportion of patients achieving the target. This short-term (1-year) cost-effectiveness analysis was conducted from the perspective of a U.S. health care payer.

RESULTS: More patients achieved HbA1c $< 7.5\%$ ($P < 0.0001$) and $< 8.0\%$ ($P = 0.0003$), and a similar percentage achieved HbA1c $\leq 9.0\%$ with IDegLira versus IGlar U100 (DUAL V). Similar proportions of patients achieved all 3 HbA1c targets with IDegLira compared with basal-bolus therapy (DUAL VII). The odds of achieving double or triple composite outcomes were significantly higher for IDegLira versus IGlar U100 or basal-bolus for all 3 HbA1c targets ($P < 0.0001$ in each case) in both trials. For each \$1 spent on IDegLira, the equivalent annual costs per patient to achieve HbA1c targets of $< 7.5\%$, $< 8.0\%$, or $\leq 9.0\%$ without hypoglycemia and without weight gain were \$2.43, \$2.10, and \$2.05, respectively, for IGlar U100 and \$6.33, \$5.80, and \$6.06, respectively, for basal-bolus therapy.

CONCLUSIONS: Based on data from DUAL V and DUAL VII, this analysis showed that a greater or similar proportion of patients with T2D reached HbA1c targets with IDegLira compared with IGlar U100/basal-bolus therapy. Odds of achieving double or triple composite outcomes of HbA1c reduction

without hypoglycemia and/or without weight gain were greatest for IDegLira. Short-term cost analyses based on the triple composite outcomes suggest that IDegLira is a cost-effective treatment option in the United States compared with either uptitration of IGlar U100 or basal-bolus therapy.

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What is already known about this subject

- Effective diabetes therapy is a delicate balance between the benefits of good glycemic control, the risk of hypoglycemia, and drug-related side effects.
- The latest guidelines for the management of type 2 diabetes (T2D) continue to recommend optimal glycemic control treatment targets but suggest individualizing hemoglobin A1c (HbA1c) targets according to factors such as age, duration of diabetes, and comorbid conditions including cardiovascular risk.

What this study adds

- In DUAL V, the odds of achieving HbA1c $< 7.5\%$ ($P < 0.0001$) and $< 8.0\%$ ($P = 0.0003$) are significantly greater with insulin degludec/liraglutide (IDegLira) than with insulin glargine 100 U/mL (IGlar U100), whereas more than 90% of patients in both treatment arms achieved HbA1c $\leq 9.0\%$. In DUAL VII, similar percentages of patients achieved HbA1c $< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$ with IDegLira compared with basal-bolus therapy.
- The odds of achieving more clinically relevant combined outcomes, in terms of either a double (HbA1c target without hypoglycemia or weight gain) or triple (HbA1c target without hypoglycemia and without weight gain) composite outcome at HbA1c targets of $< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$ was significantly greater with IDegLira than with both IGlar U100 and basal-bolus therapy in DUAL V and DUAL VII, respectively.
- In the present short-term analysis, IDegLira was found to be cost-effective versus continued uptitration of IGlar U100 and basal-bolus therapy in patients, with T2D failing to achieve glycemic targets on basal insulin alone.

The latest guidelines for the management of type 2 diabetes (T2D) continue to recommend optimal glycemic control treatment targets but suggest individualizing hemoglobin A1c (HbA1c) targets according to factors such as age, duration of diabetes, and comorbid conditions, including cardiovascular risk.¹⁻⁵ Evidence suggests that approximately 50% of patients with T2D have HbA1c levels $>7.0\%$,^{6,7} and many do not achieve more lenient targets such as HbA1c $<8.0\%$.⁸ Factors contributing to suboptimal glycemic control include poor treatment adherence and clinical inertia, that is, when health care providers do not respond quickly enough to evidence of poor glycemic control.⁹⁻¹¹ A recent review reported that time to treatment intensification for patients with HbA1c $\geq 8.0\%$ was 3.2-4.9 years depending on their current treatment regimen.¹⁰ Barriers to treatment intensification include costs,¹² patient adherence to more complicated treatment regimens,¹² and physician concerns regarding potential treatment-related side effects, particularly weight gain and hypoglycemia.¹³

Health care management requires balancing effectiveness with cost, and it is increasingly important for new interventions to represent good value in this challenging economic environment. Long- and short-term cost-effectiveness analyses have been conducted for insulin degludec/liraglutide (IDegLira) compared with 3 other basal intensification strategies: uptitration of insulin glargine 100 units/mL (IGlar U100), addition of liraglutide to a basal insulin regimen (as separate components), and basal-bolus therapy with IGlar U100+insulin aspart (IAsp).¹⁴⁻¹⁸ These analyses demonstrated that IDegLira is a cost-effective treatment option in patients with uncontrolled T2D from a health care payer perspective in a number of countries.^{14,15,17-23} Regarding cost per patient achieving treatment target (cost of control), short-term analyses reported lower or equivalent annual costs of control with IDegLira compared with basal-bolus therapy or basal insulin uptitration, both for glycemic targets (HbA1c $\leq 6.5\%$ or $<7.0\%$) singularly and for composite outcomes without hypoglycemia and/or weight gain.^{16,24}

With T2D management guidelines recommending optimal HbA1c targets that must be individualized, taking into account multiple factors, HbA1c targets used in clinical practice and for quality metrics, for example, the Healthcare Effectiveness Data and Information Set (HEDIS), may be higher than those used in clinical trials.^{25,26} For example, the consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for management of hyperglycemia in T2D states that an HbA1c target of $\leq 7\%$ is reasonable for nonpregnant adults who could expect to gain microvascular benefits with long-term intensive control, but higher glycemic targets could be considered based on patient preferences and goals; risk of adverse effects (e.g., hypoglycemia, weight gain); and patient characteristics, including frailty and comorbidities.⁴ Furthermore, HEDIS defines poor glycemic control as HbA1c $>9\%$ and glycemic control as HbA1c $<8\%$ or $<7\%$,²⁶ with individual targets dependent on the individual patient's circumstances.

Patients and physicians are likely to be more motivated to intensify treatment in a timely manner if they are able to initiate agents that improve glycemic control with a low risk of side effects and without increasing regimen complexity. Therefore, the availability of such agents could improve patient outcomes. IDegLira is a once-daily, fixed-ratio combination of the basal insulin degludec and the glucagon-like peptide-1 receptor agonist liraglutide.²⁷⁻³³ The clinical utility of IDegLira has been investigated in the DUAL clinical trial program and real-world studies.²⁷⁻³⁶ In patients with HbA1c 7%-10%, the DUAL V study demonstrated that IDegLira was superior to uptitrated IGlar U100 (20-50 units plus metformin $\geq 1,500$ mg/day) in HbA1c reduction, risk of hypoglycemia, and change in body weight.³¹ The DUAL VII study, in a similar patient set (HbA1c 7%-10%; on 20-50 units of IGlar U100 and metformin), confirmed noninferiority of IDegLira versus basal-bolus therapy (IGlar U100+IAsp ≤ 4 times daily) in lowering HbA1c, and demonstrated superiority of IDegLira versus basal-bolus in hypoglycemia risk and change in body weight.²⁷ Notably, the greater HbA1c reduction with IDegLira versus IGlar U100 in DUAL V and the similar HbA1c improvement with IDegLira versus basal-bolus in DUAL VII, after 26 weeks of treatment, were independent of baseline HbA1c, confirming that IDegLira is effective across a broad range of patients.^{37,38} In both trials, a greater proportion of patients achieved the composite outcomes of HbA1c $\leq 6.5\%$ or $<7.0\%$ without hypoglycemia and/or weight gain with IDegLira versus comparator.^{31,37} Attainment of a broader range of HbA1c targets has not yet been investigated.

This post hoc analysis explored whether patients receiving IDegLira were more likely to achieve composite outcomes, including HbA1c targets of $<7.5\%$, $<8.0\%$, and $\leq 9.0\%$, that are often used in clinical practice and for quality metrics in combination with hypoglycemia and/or weight gain, compared with uptitrated IGlar U100 or basal-bolus therapy, after 26 weeks of treatment. Short-term cost-effectiveness of IDegLira versus uptitrated IGlar U100 or basal-bolus therapy for the triple composite outcome using each of the HbA1c targets was also analyzed targets, from a U.S. health care payer perspective.

Methods

Study Design and Participants

The data reported in this analysis were obtained from the phase 3 DUAL V (NCT01952145) and DUAL VII (NCT02420262) trials; both have been described previously.^{27,31} Briefly, adults with uncontrolled T2D (HbA1c 7%-10%) on 20-50 units of IGlar U100+metformin and with body mass index ≤ 40 kg/m² were randomized 1:1 to receive IDegLira or comparator treatment (IGlar U100 [DUAL V] or IGlar U100+IAsp [DUAL VII]) alongside pretrial metformin for 26 weeks.^{27,31}

In both trials, patients initiated IDegLira at 16 units (16 U insulin degludec/0.58 mg liraglutide) and were uptitrated to a maximum dose of 50 units (50 U insulin degludec/1.8 mg liraglutide).^{27,31} IGlar U100 was initiated at the pretrial basal insulin dose, either alone (DUAL V) or as part of a basal-bolus

regimen (DUAL VII), with no maximum daily dose.^{27,31} Both IDegLira and IGlir U100 were titrated twice weekly targeting a fasting self-monitored blood glucose (SMBG) of 72-90 mg/dL. In DUAL VII, IAsp was initiated from the day of randomization at a starting dose of 4 U per main meal (≤ 4 times per day) and titrated twice weekly, aiming for a mean preprandial and bedtime SMBG target of 72-108 mg/dL.^{27,31}

In DUAL V, confirmed hypoglycemic episodes were defined as those requiring external assistance and/or plasma glucose < 56 mg/dL. In DUAL VII, treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycemic episodes were defined as episodes requiring external assistance and/or with plasma glucose < 56 mg/dL accompanied by glycopenic symptoms.^{27,31}

Both trials were conducted in accordance with International Conference on Harmonization Good Clinical Practice and the Declaration of Helsinki.^{39,40}

Post Hoc Analysis

The analysis compared the percentage of patients in each trial reaching the following targets after 26 weeks: HbA1c $< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$ and the double or triple composite outcomes of achieving HbA1c targets without hypoglycemia and/or weight gain. The following composite outcomes were assessed: (a) double composite outcome of achieving each of the HbA1c targets ($< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$) without hypoglycemia; (b) double composite outcome of achieving each of the HbA1c targets ($< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$) without weight gain; and (c) triple composite outcome of achieving each of the HbA1c targets ($< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$) without hypoglycemia and without weight gain. To attain each composite outcome, patients were required to achieve every component of the outcome by end of trial (i.e., HbA1c $< 7.5\%$, $< 8.0\%$, or $\leq 9.0\%$ at week 26; no hypoglycemia in the past 12 weeks; and unchanged or reduced body weight compared with baseline). Only hypoglycemic events during the past 12 weeks were included, in keeping with the original trials,^{27,31} as this was considered a maintenance period with more stable insulin doses and glycemic control, thus allowing fair and meaningful comparison of hypoglycemia rates between treatment arms, as opposed to the initial titration period where doses were increased based on individual titration. DUAL V and DUAL VII were analyzed separately. Attainment of treatment targets were analyzed using a logistic regression model, including treatment and region as fixed factors and baseline HbA1c (and baseline body weight where applicable) as covariates. Missing data were imputed using last observation carried forward in DUAL V and a mixed model for repeated measurements in DUAL VII.

Cost-Effectiveness Analysis

The cost per patient achieving target (cost of control) was calculated for the following 3 outcomes: (a) HbA1c $< 7.5\%$ without hypoglycemia and without weight gain, (b) HbA1c $< 8.0\%$ without hypoglycemia and without weight gain, and

(c) HbA1c $\leq 9.0\%$ without hypoglycemia and without weight gain. Cost of control for each outcome with each intervention (in 2017 U.S. dollars) was calculated using an economic model developed in Microsoft Excel (Microsoft, Redmond, WA). Using this model, the cost per patient achieving each target with the 2 interventions was calculated by dividing annual cost of treatment by the proportion of patients achieving each target. The number of patients needed to treat with IDegLira to bring 1 patient to target across all HbA1c targets ($< 7.5\%$, $< 8.0\%$, and $\leq 9.0\%$) without weight gain and without hypoglycemia was also calculated as the reciprocal of the percentage of patients achieving the composite outcome.^{41,42} The spending required with the comparator treatment to bring 1 patient to target relative to \$1 spent on IDegLira was calculated by dividing the cost of control with the comparator by the cost of control with IDegLira. Appendix A provides a summary of these calculations (available in online article). Analyses were calculated over a 1-year time period; therefore, no discounting was applied. This is aligned with the time period over which many health plan budgets are calculated in the United States.^{16,43}

For the purpose of this analysis, annual treatment costs included the costs of medication (acquisition cost), needles for subcutaneous injection, and SMBG testing. Treatment costs were based on the perspective of a third-party payer in the United States. SMBG testing was based on an analysis of insurance claims in the United States adjusted to 2017 values using the Consumer Price Index for medical care, with calculations for basal insulin regimens applied to IDegLira and IGlir U100 and those for basal-bolus regimens applied to IGlir U100 + IAsp.⁴⁴ For medication costs, IDegLira and IGlir U100 doses were taken from the end of the DUAL V study,³¹ and IDegLira, IGlir U100, and IAsp doses were taken from the end of the DUAL VII study.²⁷ These doses were used to calculate daily costs of treatment with each therapy based on published wholesale acquisition costs.⁴⁵ It was assumed that patients receiving basal insulin used 1 needle per day (IDegLira: NovoFine; IGlir U100: BD MicroFine), and patients receiving basal-bolus therapy used 4 needles per day (1 BD MicroFine and 3 NovoFine). The estimated daily costs were multiplied by 365.25 to estimate annual costs.⁴³

Sensitivity Analyses

Sensitivity analyses were conducted to assess how variation in the model inputs impacted cost-effectiveness outcomes. The cost of medication, needles, and SMBG testing, as well as proportion of patients achieving targets were increased and decreased by 10% in turn. Other analyses assessed the impact of variations in the cost of comparator insulins, by applying biosimilar IGlir U100 costs and twice-daily dosing of IGlir U100. An analysis was also conducted with cost of control assessed over 6 months rather than 1 year, because both trials were 26 weeks.

A probabilistic sensitivity analysis was also conducted. The proportion of patients achieving each target and annual costs

FIGURE 1

Odds of Patients in DUAL V Achieving HbA1c <7.5%, <8.0%, and ≤9.0%, Double Composite Outcomes of HbA1c Targets Without Confirmed Hypoglycemia^a or Weight Gain, and Triple Composite Outcome of HbA1c Targets Without Confirmed Hypoglycemia^a and Without Weight Gain After 26 Weeks of Treatment with IDegLira Versus IGlir U100

^aOccurring in the last 12 weeks of treatment. The binary outcome was analyzed using a logistic regression model with logit link. The model included treatment and region as fixed factors and baseline HbA1c and baseline bodyweight (where relevant) values as covariates. Missing data are imputed using last observation carried forward. Hypoglycemia: confirmed episode where subject unable to self-treat and/or have a recorded plasma glucose <56 mg/dL. CI=confidence interval; HbA1c=glycated hemoglobin; IDegLira=insulin degludec/liraglutide; IGlir U100=insulin glargine 100 units/mL; OR=odds ratio.

were sampled for each intervention from normal distributions. Following sampling of values for both treatments, the therapy with the lowest cost of control for each target was recorded. The process was then repeated 1,000 times, as outcomes were stable at these settings, with all inputs resampled for each iteration.

Results

HbA1c Targets

In DUAL V, the odd ratios (ORs) of achieving HbA1c <7.5% (OR=3.57, 95% confidence interval [CI]=2.27-5.62; P<0.0001) and <8.0% (OR=2.92, 95% CI=1.63-5.21; P=0.0003) were significantly greater with IDegLira than with IGlir U100 (Figure 1). However, the OR of achieving HbA1c ≤9.0% was not significantly different between the same treatments (OR=1.34, 95% CI=0.46-3.93). In DUAL VII, similar percentages of patients achieved HbA1c <7.5%, <8.0%, and ≤9.0% with IDegLira (82.8%, 91.6%, and 99.2%, respectively) compared with basal-bolus therapy (83.7%, 93.1%, and 98.7%, respectively; Table 1), corresponding to nonsignificant ORs (Figure 2).

In both trials, >70% of patients in both treatment arms had HbA1c ≤9.0% at baseline due to the inclusion/exclusion criteria (HbA1c 7%-10%). As a result, a similarly high percentage

(>95%) of patients in both treatment arms achieved HbA1c ≤9.0% by week 26 (Table 1).

Composite Outcomes

The odds of achieving the double composite outcomes (achieving any HbA1c target [<7.5%, <8.0%, or ≤9.0%] either without hypoglycemia or without weight gain) were significantly higher for IDegLira than for IGlir U100 in DUAL V (Figure 1) and basal-bolus therapy in DUAL VII (Figure 2; P<0.0001 for all HbA1c targets in both studies).

Across all HbA1c targets, the odds of achieving the triple composite outcome (reaching each HbA1c target without hypoglycemia and without weight gain) were significantly higher for IDegLira than for comparator in both trials (Figures 1 and 2; P<0.0001 for all HbA1c targets in both trials).

Cost-Effectiveness Analysis Based on Patients Achieving the Triple Composite Outcome

Annual Costs. Annual treatment costs for patients receiving IDegLira were similar in the 2 trials due to the similar mean doses of IDegLira received. In DUAL V, the annual treatment cost was \$11,180 per patient receiving IDegLira compared with \$7,682 per patient receiving IGlir U100. In DUAL VII,

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TABLE 1 Percentage of Patients in DUAL V and DUAL VII Achieving HbA1c <7.5%, <8.0%, and ≤9.0% at Baseline and After 26 Weeks

	DUAL V				DUAL VII			
	IDegLira (n = 278)		IGlar U100 (n = 279)		IDegLira (n = 252)		Basal-Bolus (n = 254)	
	Baseline	Week 26	Baseline	Week 26	Baseline	Week 26	Baseline	Week 26
HbA1c, mean (SD), % ^{27,31}	8.4 (0.9)	6.6 (0.9)	8.2 (0.9)	7.1 (0.9)	8.2 (0.8)	6.7 (0.8)	8.2 (0.8)	6.7 (0.8)
Patients achieving HbA1c <7.5%, %	18.3	85.6	18.3	67.4	16.3	82.8	19.7	83.7
Patients achieving HbA1c <8.0%, %	36.0	92.1	40.5	83.2	40.5	91.6	39.4	93.1
Patients achieving HbA1c ≤9.0%, %	74.5	97.5	81.4	96.8	85.3	99.2	81.9	98.7

Note: Data are based on observed values from the full analysis set. In DUAL V, missing data are imputed using last observation carried forward. HbA1c = glycated hemoglobin; IDegLira = insulin degludec/liraglutide; IGlar U100 = insulin glargine 100 units/mL; SD = standard deviation.

annual treatment costs were \$10,973 per patient on IDegLira and \$11,778 for those on basal-bolus therapy (Appendix B, available in online article). In DUAL V, the higher acquisition cost of IDegLira (\$10,343) compared with IGlar U100 (\$6,871) was responsible for most of the difference in annual treatment costs between treatments (Appendix B). In DUAL VII, acquisition costs were comparable between the 2 treatments (IDegLira, \$10,135; basal-bolus, \$9,848), but greater use of diabetes-related consumables (needles and SMBG tests) in the basal-bolus arm contributed to the higher overall annual treatment costs versus IDegLira.

Number Needed to Treat. The number of patients needed to treat with IDegLira to bring 1 patient to target across all HbA1c targets (<7.5%, <8.0%, and ≤9.0%) without weight gain or without hypoglycemia in both trials was consistently lower than with the comparator treatment. For DUAL V, the number of patients needed to treat with IDegLira to bring 1 patient to HbA1c <7.5% was 2.13, compared with 7.52 patients on IGlar U100 (Appendix B). Similarly, the number of patients needed to treat to bring 1 patient to target was lower with IDegLira versus IGlar U100 for HbA1c <8.0% (IDegLira, 2.00; IGlar U100, 6.10) and ≤9.0% (IDegLira, 1.87; IGlar U100, 5.59). For DUAL VII, the number of patients needed to treat to bring 1 patient to HbA1c <7.5% was 2.12 with IDegLira compared with 12.50 with basal-bolus therapy. Likewise, a smaller number needed to treat was seen for IDegLira versus basal-bolus therapy to bring 1 patient to HbA1c <8.0% (IDegLira, 1.90; basal-bolus, 10.42) and ≤9.0% (IDegLira, 1.77; basal-bolus, 10.00).

Cost of Control. For both trials, the annual cost per patient achieving each of the 3 HbA1c targets without hypoglycemia and without weight gain was lower with IDegLira than IGlar U100 and basal-bolus therapy (Figure 3). Based on DUAL V, for each \$1 spent on IDegLira, the equivalent costs for IGlar U100 to achieve HbA1c <7.5%, <8.0%, or ≤9.0% without hypoglycemia and without weight gain were \$2.43, \$2.10, and \$2.05 per patient, respectively (Appendix A). Based on DUAL VII, the equivalent annual cost per patient achieving HbA1c <7.5%, <8.0%, or ≤9.0% without hypoglycemia and without weight

gain was \$6.33, \$5.89, and \$6.06, respectively, for basal-bolus therapy for each \$1 spent on IDegLira (Appendix A).

Sensitivity Analyses

The cost of control was lower with IDegLira versus comparator in all sensitivity analyses (data not shown); findings were not impacted by variations (±10%) in the proportion of patients achieving each treatment target and the treatment costs applied, applying alternative costs for comparator insulins, or calculating cost of control over 6 months.

Probabilistic sensitivity analysis, with sampling around clinical and cost inputs, found that the probability that IDegLira was associated with a lower cost of control than comparator was 100% for all targets, confirming the results of the base case analysis.

Discussion

The novelty of the present analysis is that it includes a broad range of HbA1c targets that are relevant to HEDIS criteria and certain clinical practice settings.²⁶ Results show that IDegLira is more efficacious than IGlar U100 and similarly effective to basal-bolus therapy in bringing patients to HbA1c treatment targets of <7.5% and <8.0%. This is consistent with primary findings from DUAL V and DUAL VII, which demonstrated superiority and noninferiority, respectively, of IDegLira versus comparator treatment in reducing HbA1c.^{27,31} In both trials, treatments were similarly effective in bringing patients uncontrolled (HbA1c 7%-10%) on IGlar U100 and metformin to HbA1c ≤9.0%, as would be expected.

Furthermore, a higher proportion of patients achieved the composite outcome of HbA1c targets without weight gain and/or hypoglycemia with IDegLira versus uptitrated IGlar U100 or basal-bolus. This reflects the wide-ranging benefits of IDegLira, targeting both glycemic control and other factors that may reduce the long-term risk of diabetes-related complications and associated costs.^{46,47} Indeed, despite higher treatment costs associated with IDegLira compared with IGlar U100, the cost of control was lowest for IDegLira across the triple composite outcome of each target HbA1c without hypoglycemia and without weight gain. It is also important to note that the

FIGURE 2

Odds of Patients in DUAL VII Achieving HbA1c <7.5%, <8.0%, and ≤9.0%, Double Composite Outcomes of HbA1c Targets Without Severe or BG Confirmed Symptomatic Hypoglycemia^a or Weight Gain, and Triple Composite Outcome of HbA1c Targets Without Severe or BG Confirmed Symptomatic Hypoglycemia^a and Without Weight Gain After 26 Weeks of Treatment with IDegLira Versus IGlir U100 plus IAsp

^aOccurring in the last 12 weeks of treatment. The binary outcome was analyzed using a logistic regression model with logit link. The model included treatment and region as fixed factors and baseline HbA1c and baseline bodyweight (where relevant) values as covariates. Missing HbA1c assessments at week 26 were imputed from the primary analysis using mixed model for repeated measurements. Hypoglycemia: episode that requires third-party assistance or is confirmed by plasma glucose <56 mg/dL with symptoms consistent of hypoglycemia.

BG=blood glucose; CI=confidence interval; HbA1c=glycated hemoglobin; IAsp=insulin aspart; IDegLira=insulin degludec/liraglutide; IGlir U100=insulin glargine 100 units/mL; OR=odds ratio.

clinical benefits of IDegLira are achieved with a simpler treatment regimen using fewer injections and dose adjustments, resulting in lower needle and SMBG costs compared with basal-bolus therapy.⁴⁸

The analysis assessed the cost per patient achieving multi-factorial treatment targets, capturing weight gain and hypoglycemia, as this represents the maximal benefit for the individual patient. The HbA1c targets were selected as they represent outcomes used in quality metrics, such as HEDIS (HbA1c=8%),² and are incorporated into programs such as the Medicare star ratings system (HbA1c=9%).⁴⁹ Furthermore, clinical guidelines now advocate that individual HbA1c targets should consider factors such as age, frailty, comorbidities, and diabetes duration. The current position statement from the ADA and EASD suggests that a more lenient target (e.g., <8%) may be adequate for older or frailer patients and those with a shorter life expectancy, long disease duration, a history of hypoglycemia, or advanced cardiovascular disease.⁴ The highest HbA1c target included in this analysis, ≤9.0%, may be relevant for patients for whom lower targets are not feasible due to associated health conditions and/or hypoglycemic unawareness. It should be

noted that this is not an optimal treatment target and other efforts to control HbA1c and cardiovascular risk should be considered.⁴

The results from the present analysis are consistent with a previous evaluation of short term cost-effectiveness of IDegLira versus IGlir U100, using the same methodology but based on HbA1c targets of ≤6.5% and <7.0%, which showed that IDegLira was associated with lower cost of control than continued uptitration of IGlir U100 in the United States, with the greatest benefits observed when the triple composite outcome was considered.¹⁶ Our results also agree with a short-term cost-effectiveness analysis of IDegLira versus basal-bolus therapy that captured the effects of insulin dosing and hypoglycemia rates in terms of costs and quality-adjusted life years (QALYs). Drummond et al. (2018) considered IDegLira a cost-effective alternative to basal-bolus therapy from the perspective of a U.K. public health care payer.¹⁵ Similarly, long-term analyses that capture glycemic control, insulin dosing, hypoglycemia rates, and the development of diabetes-related complications have reported that IDegLira is a cost-effective treatment intensification option in patients with uncontrolled

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FIGURE 3 Cost of Control for Patients Achieving Target HbA1c <7.5%, <8.0%, or ≤9.0% Without Hypoglycemia and Without Weight Gain for Patients on IDegLira or IGLar U100 (DUAL V) and on IDegLira IGLar U100 plus IAsp (DUAL VII)^a

Cost per patient achieving control, \$	DUAL V		DUAL VII	
	IDegLira	IGlar U100	IDegLira	IGlar U100+IAsp
<7.5% with no hypoglycemia and no weight gain	23,788	57,761	23,248	147,227
<8.0% with no hypoglycemia and no weight gain	22,316	46,843	20,821	122,689
≤9.0% with no hypoglycemia and no weight gain	20,937	42,917	19,421	117,781

^aCosts are shown in 2017 U.S. dollars.

HbA1c = glycated hemoglobin; IAsp = insulin aspart; IDegLira = insulin degludec/liraglutide; IGLar U100 = insulin glargine 100 units/mL.

T2D compared with other basal intensification strategies (up-titration of IGLar U100, addition of liraglutide to a basal insulin regimen [as separate components], and basal-bolus therapy with IGLar U100+IAsp).^{14,17-19} The long-term cost-effectiveness of IDegLira in the United States compared with IGLar U100 or IGLar U100+IAsp was demonstrated based on projections of clinical outcomes and direct costs using the IQVIA CORE Diabetes Model^{19,50}; key drivers of IDegLira cost-effectiveness were greater reduction in HbA1c compared with IGLar U100,¹⁷ and the lower acquisition cost and reduced costs of treating diabetes-related complications versus basal-bolus therapy.¹⁹ Furthermore, an analysis based on pooled patient-level data demonstrated that IDegLira was more effective and less costly

versus the free combination of basal insulin and liraglutide.¹⁴ Given budget constraints of health care payers, the importance of treatments representing good value for money to maximize outcomes with limited resources cannot be underestimated.⁵¹ Cost-effectiveness analyses therefore provide important information to help health care payers in deciding how best to allocate resources to achieve maximal health care gains within a limited budget.^{52,53} Considering the abundance of short- and long-term evidence, as well as the results of the present analysis, IDegLira appears to offer a highly cost-effective intensification strategy for patients uncontrolled on basal insulin.

The present analysis can be readily replicated and updated in the event that the acquisition costs of interventions change or new data (clinical trials, meta-analyses, or additional post hoc analyses) become available. Additionally, the simplicity of short-term cost-effectiveness analyses allows results to be easily interpreted, with fewer assumptions than for long-term analyses that project clinical and cost outcomes over patient lifetimes, requiring assumptions around changes in risk factors over time (e.g., HbA1c, systolic blood pressure, serum lipids, and body weight) and durability of treatment.³ Such analyses therefore become complex, compared with this approach.

Limitations

Our analysis has several limitations. As with all clinical trials, caution must be taken when generalizing these results from patients who met predefined eligibility criteria, to a broader population who may have HbA1c >10% and be uncontrolled on >50 units of basal insulin. Furthermore, these statistical analyses were not prespecified, a drawback inherent to all post hoc analyses.

Limitations of our cost-analysis methodology have been described previously.¹⁶ It uses a simple economic model and as such, incremental cost-effectiveness ratios (ICERs) in the form of cost per QALY gained are not reported. Additionally, it assumed that costs due to hypoglycemia and acute diabetes-related complications were similar for all 3 treatment regimens. However, other economic models that do incorporate the cost of these complications and report ICERs have been published for DUAL V, DUAL VII, and pooled trial data.¹⁷⁻¹⁹ Furthermore, patient-reported outcomes for the DUAL V and DUAL VII trials are reported elsewhere.^{31,54} The results from the present analysis are not designed to replace previously published reports on the long-term cost-effectiveness of IDegLira, or to capture the impact of IDegLira on quality of life compared with other insulin strategies, but to complement these data and inform health care payers of the short-term costs involved.

It is also important to note that the cost analysis is based on the attainment of treatment targets, but there is no clear difference in treatment costs between patients who have HbA1c levels of 7.4% and 7.5%, for example. However, the impact of treating a continuous outcome as an arbitrary outcome on the results is likely to be that it has provided a conservative estimate of the cost-effectiveness of IDegLira.

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In line with most cost-effectiveness analyses, our study assumed 100% treatment adherence to all medications, which may have led to an overestimation of pharmacy costs and, therefore, costs of control. Similarly, the clinical outcomes entered into this economic model were based on clinical trial data and the proportion of patients achieving treatment targets may vary in clinical practice. However, these limitations are common to most cost-effectiveness modeling, and the assumption of 100% adherence was applied in all treatment arms, providing a fair comparison of therapies.

Finally, it is recognized that cost discounting or rebates occurring in real life between health care plans and manufacturers may lead to lower wholesale costs than used in the present analysis.

Conclusions

The analysis showed that across a broad range of HbA1c targets (<7.5%, <8.0%, and ≤9.0%), including those relevant to HEDIS criteria and certain clinical practice settings, the odds of achieving composite outcomes of HbA1c targets without hypoglycemia and/or weight gain was significantly greater with IDegLira versus IGLar U100 and basal-bolus therapy, based on data from DUAL V and DUAL VII, respectively. Evaluation of short-term cost-effectiveness of IDegLira versus continued uptitration of IGLar U100 or basal-bolus therapy for triple composite outcomes showed lower cost of control values for IDegLira. These data suggest that IDegLira is a cost-effective treatment option for patients uncontrolled on basal insulin in the United States, compared with either uptitration of IGLar U100 or basal-bolus therapy.

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DISCLOSURES

This study was supported by Novo Nordisk A/S. The analysis was based on the DUAL V (NCT01952145) and DUAL VII (NCT02420262) trials, which were funded and conducted by Novo Nordisk. This post hoc analysis was conceived and interpreted by the authors and drafted with medical writing support that was funded by Novo Nordisk. Novo Nordisk also reviewed the manuscript for medical accuracy.

Hunt and Malkin are employees of Ossian Health Economics and Communications, which received consulting fees from Novo Nordisk during the conduct of this study and has received consulting fees from Novo Nordisk, unrelated to this study. Mocarski, Ranthe, and Schiffman are employees of Novo Nordisk and Novo Nordisk A/S. Cannon has received speaker fees/honoraria from Abbvie, Amgen, and Janssen; speaker fees from Novo Nordisk; and has stock ownership in Novo Nordisk. Bargiota has received speaker fees/honoraria from AstraZeneca, Eli Lilly, MSD, Novo Nordisk, Sanofi, Boehringer Ingelheim, and Novartis. Billings has received personal fees from Novo Nordisk, Sanofi, and Dexcom, unrelated to this study. Leiter reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, Servier, and GSK, unrelated to this study. Doshi has no relevant conflicts of interest to disclose.

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APPENDIX A Summary of Calculations Used to Estimate the Cost of Control (Achievement of Triple Composite Outcomes) for Patients Enrolled in DUAL V and DUAL VII

	DUAL V			DUAL VII		
	IDegLira n = 278	IGlar U100 n = 279	Interpretation	IDegLira n = 252	Insulin Glargine U100 + IAsp n = 254	Interpretation
Annual treatment cost ^a (\$)	11,180	7,682	Annual treatment cost is \$3,498 higher for IDegLira than for IGlar U100	10,973	11,778	Annual treatment cost is \$805 lower for IDegLira than for basal-bolus
Treatment cost index	11,180 ÷ 7,682 = 1.46	7,682 ÷ 7,682 = 1.00	IDegLira is 46% more costly than IGlar U100 on an annual per patient basis	10,973 ÷ 11,778 = 0.93	11,778 ÷ 11,778 = 1.00	IDegLira is 7% less costly than basal-bolus on an annual per patient basis
Treatment efficacy (% of patients achieving control)						
<7.5%	47.0	13.3		47.2	8.0	
<8.0%	50.1	16.4		52.7	9.6	
≤9.0%	53.4	17.9		56.5	10.0	
Treatment efficacy index						
<7.5%	47.0 ÷ 13.3 = 3.5		IDegLira is 3.5-, 3.1-, and 3.0-fold more effective in bringing patients to HbA1c <7.5%, 8.0%, and ≤9.0% than IGlar U100	47.2 ÷ 8.0 = 5.9		IDegLira is 5.9-, 5.5-, and 5.7-fold more effective in bringing patients to HbA1c <7.5%, 8.0%, and ≤9.0% than basal-bolus
<8.0%	50.1 ÷ 16.4 = 3.1			52.7 ÷ 9.6 = 5.5		
≤9.0%	53.4 ÷ 17.9 = 3.0			56.5 ÷ 10.0 = 5.7		
Cost per patient: achieving control (\$)						
<7.5%	11,180 ÷ 47.0 × 100 = 23,788	7,682 ÷ 13.3 × 100 = 57,761		10,973 ÷ 47.2 × 100 = 23,248	11,778 ÷ 8.0 × 100 = 147,227	
<8.0%	11,180 ÷ 50.1 × 100 = 22,316	7,682 ÷ 16.4 × 100 = 46,843		10,973 ÷ 52.7 × 100 = 20,821	11,778 ÷ 9.6 × 100 = 122,689	
≤9.0%	11,180 ÷ 53.4 × 100 = 20,937	7,682 ÷ 17.9 × 100 = 42,917		10,973 ÷ 56.5 × 100 = 19,421	11,778 ÷ 10.0 × 100 = 117,781	
Cost of control index						
<7.5%	23,788 ÷ 57,760 = 0.41		IDegLira costs approximately half of the amount of IGlar U100 to achieve the same outcome	23,248 ÷ 147,227 = 0.16		IDegLira costs approximately one sixth of the amount of basal-bolus to achieve the same outcome
<8.0%	22,316 ÷ 46,842 = 0.48			20,821 ÷ 122,689 = 0.17		
≤9.0%	20,937 ÷ 42,917 = 0.49			19,421 ÷ 117,781 = 0.16		
Amount spent to achieve target relative to \$1 spent on IDegLira						
<7.5%	57,760 ÷ 23,788 = 2.43		For every \$1 spent on IDegLira, \$2.43, \$2.10, and \$2.05 is spent on IGlar U100 to bring 1 patient to control at <7.5%, <8.0%, and ≤9.0%, respectively.	147,227 ÷ 23,248 = 6.33		For every \$1 spent on IDegLira, \$6.33, \$5.89, and \$6.06 is spent on basal-bolus to bring 1 patient to control at <7.5%, <8.0%, and ≤9.0%, respectively
<8.0%	46,842 ÷ 22,316 = 2.10			122,689 ÷ 20,821 = 5.89		
≤9.0%	42,917 ÷ 20,937 = 2.05			117,781 ÷ 19,421 = 6.06		

^aTreatment costs are shown to nearest integer for ease of reading, but calculations are based on values to 2 decimal places; calculations may not sum exactly due to rounding. Costs are shown in 2017 U.S. dollars.

HbA1c = glycated hemoglobin; IAsp = insulin aspart; IDegLira = insulin degludec/liraglutide; IGlar U100 = insulin glargine 100 units/mL.

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APPENDIX B Annual Cost Outcomes for Patients and Number Needed to Treat to Bring Patients to Target (<7.5%, <8.0%, and ≤9.0%) for Patients on IDegLira Versus IGlir U100 (DUAL V) and for Patients on IDegLira Versus IGlir U100 Plus IAsp (DUAL VII)

	DUAL V			DUAL VII		
	IDegLira n = 278	IGlar U100 n = 279	Difference	IDegLira n = 252	IGlar U100 plus IAsp n = 254	Difference
Annual costs^a (\$)						
Medication	10,343	6,871	+3,471	10,135	9,848	+287
Needle	186	159	+27	186	719	-532
SMBG	651	651	0	651	1,212	-560
Total	11,180	7,682	+3,498	10,973	11,778	-805
Number needed to treat to bring patients to HbA1c target (<7.5%, <8.0%, and ≤9.0) without hypoglycemia or weight gain						
<7.5%	2.13	7.52	-5.39	2.12	12.50	-10.38
<8.0%	2.00	6.10	-4.10	1.90	10.42	-8.52
≤9.0%	1.87	5.59	-3.71	1.77	10.00	-8.23

Note: Columns may not sum exactly due to rounding.

^aAnnual treatments costs based on the following acquisition costs: IDegLira (Xultophy) 1,500 U at \$1,039.00; IGlir U100 (Lantus) 1,500 U at \$425.31; IAsp (NovoLog) 1,500 U at \$558.83; NovoFine 100 needles at \$51.04 and BD UltraFine Nano 100 needles at \$43.64. Costs are shown in 2017 U.S. dollars.

HbA1c = glycated hemoglobin; IAsp = insulin aspart; IDegLira = insulin degludec/liraglutide; IGlir U100 = insulin glargine 100 units/mL; SMBG = self-monitored blood glucose.