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BRIEF REPORT

Efficacy and Safety of IDegLira in Participants with Type 2 Diabetes in India Uncontrolled on Oral Antidiabetic Drugs and Basal Insulin: Data from the DUAL Clinical Trial Program

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ABSTRACT

Introduction: The efficacy and safety of insulin degludec/liraglutide (IDegLira) has been evaluated in the Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes (DUAL) phase 3 clinical trial program. In this post hoc analysis, we compared the efficacy and safety of IDegLira in the Indian subpopulation with the results from the global trial population of DUAL trials. The analysis includes participants uncontrolled on oral antidiabetic drugs (OADs) in DUAL I and DUAL IV and participants uncontrolled on basal insulin and OADs in DUAL II.

Methods: Three phase 3 trials were included in the analysis: DUAL I extension (IDegLira vs. insulin degludec or liraglutide 1.8 mg in participants uncontrolled on metformin ± pioglitazone; 52 weeks; $n = 1663$), DUAL IV (IDegLira vs. placebo as an add-on to a regimen of sulfonylurea ± metformin; 26 weeks; $n = 435$) and DUAL II (IDegLira vs. insulin degludec in participants uncontrolled on basal insulin + OADs; 26 weeks; $n = 398$). There were 251, 64 and 64 participants, respectively, at the Indian sites.

Results: In the Indian subpopulations, the reductions in glycated hemoglobin (HbA$_{1c}$) with IDegLira were substantial [DUAL I: 1.96% (-21 mmol/mol); DUAL IV: -1.40% (-15 mmol/mol); DUAL II: -2.20% (-24 mmol/mol)] and significantly greater than those in the comparators in each trial. IDegLira was generally weight-neutral after the administration of OADs (-0.3 and $+0.6$ kg in DUAL I and DUAL IV) and resulted in weight loss after the administration of basal insulin (-2.1 kg in DUAL II). Hypoglycemia rates were 1.98, 1.08 and 0.37 events/patient-years of exposure (PYE) for IDegLira, insulin degludec and liraglutide in DUAL I, 4.06 and 0.36 events/PYE for IDegLira and placebo in DUAL IV and 1.16 and 0.83

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events/PYE with IDegLira and insulin degludec in DUAL II.

Conclusions: Results from the Indian subpopulations reflect those of the global study populations, supporting IDegLira as an effective and safe treatment option for people with type 2 diabetes inadequately controlled on OADs or basal insulin + OADs in the South Asian population.

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Keywords: IDegLira; Indian population; Type 2 Diabetes

INTRODUCTION

India has the second highest number of people with diabetes worldwide, with approximately 8.6% of the population reported to have this disease [1]. Glycemic control is poor in Indian diabetic patients, with a mean glycated hemoglobin (HbA_{1c}) of $8.9 \pm 2.1\%$ (74 ± 23 mmol/mol) and only 19.7% of the Indian diabetic population achieving the American Diabetes Association/European Association for the Study of Diabetes HbA_{1c} target of <7% (<53 mmol/mol) [2, 3]. In addition to the increased prevalence of diabetes, higher rates of diabetes-related complications and mortality are also observed in South Asian people [4]. The factors contributing to this situation are multifactorial and include a genetic predisposition to diabetes, increased visceral adiposity and insulin resistance in this population, which are compounded by lifestyle factors [5]. Despite these numbers, South Asian participants in trials of glucose-lowering therapies are under-represented [6]; hence, it is important to report trial data from diverse populations.

IDegLira is a novel, once-daily, titratable, fixed-ratio combination of insulin degludec (IDeg) and the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide (Lira) that has been developed for the treatment of people with type 2 diabetes [7–9]. Importantly, GLP-1RAs act in a glucose-dependent manner and are also commonly associated with a low risk of hypoglycemia and weight loss [10]. The efficacy and safety of IDegLira and the benefits of its complementary mode of action have been examined in the large global DUAL clinical trial program [7–9, 11]. Here we describe a post hoc analysis of the efficacy and safety of IDegLira in participants from Indian trial sites included in the DUAL program. Our hypothesis was that the safety and efficacy of IDegLira in the Indian subpopulation would be similar to that demonstrated for the global population.

METHODS

This post hoc analysis used data from the IDegLira (Novo Nordisk, Bagsværd, Denmark) phase 3 trials which included participants with type 2 diabetes from Indian trial sites, namely, the DUAL I extension (52 weeks of data), DUAL IV and DUAL II trials, which included Indian sites [8, 9, 11].

Study Designs

The study designs of DUAL I extension, DUAL II and DUAL IV have been described previously [8, 9, 11] and include participants uncontrolled on oral antidiabetic drugs (OADs; DUAL I extension and DUAL IV) and participants uncontrolled on basal insulin + OADs (DUAL II). The aim of DUAL I extension was to investigate the efficacy and safety of IDegLira versus its individual components IDeg or Lira alone in participants inadequately controlled by metformin ± pioglitazone over 52 weeks [8]. In DUAL IV IDegLira was compared with placebo, both added on to a therapeutic regimen of sulphonylurea ± metformin [9], and in DUAL II, IDegLira was compared to IDeg (maximum dose of 50 U) in participants inadequately controlled on 20–40 U of basal insulin + one to two OADs [11]. Owing to differences in trial design, individual trial data were analyzed separately, rather than pooling the IDegLira data.

Endpoints and Statistical Analyses

The primary endpoint in each study was change from baseline in HbA_{1c}. Secondary efficacy endpoints included participants achieving a HbA_{1c} of <7% (<53 mmol/mol), change in body weight, insulin dose and laboratory-measured fasting plasma glucose (FPG). Safety endpoints included adverse events (AEs) and confirmed hypoglycemia [severe (unable to self-treat) and/ or plasma glucose level of <3.1 1 mmol/L]. Change from baseline in HbA_{1c}, FPG and body weight were analyzed using an analysis of covariance (ANCOVA) model with treatment and pre-trial medication as fixed factors, and baseline HbA_{1c} stratum (DUAL I only), sub-study (DUAL I only) and baseline value as covariates—all performed on the full analysis set using last observation carried forward (LOCF) method to impute missing values. Attainment of a HbA_{1c} level of <7% was analyzed using a logistic regression model (with LOCF), with the same explanatory variables as used for the primary endpoint. The results of the analyses were also summarized descriptively for other endpoints (insulin dose, rates of hypoglycemia and other safety endpoints).

As a post hoc analysis, the original individual trials were not powered to perform statistical analyses in the Indian subpopulations. The study reported here is based on a post hoc analysis of previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

The Indian subpopulations comprised 15, 16 and 15% of the global trial populations of the DUAL I extension, DUAL II and DUAL IV trials, corresponding to 251, 64 and 64 participants, respectively. Baseline characteristics of the global trial populations and Indian subpopulations are shown in Table 1. Overall, the baseline characteristics of the Indian subpopulations were largely comparable to those of the global trial populations, although the Indian participants had lower FPG and body mass index (BMI).

Glucose Control

The change in HbA_{1c} from baseline and end-of-trial HbA_{1c} in the global study populations and the Indian subpopulations from the three studies are shown by patient population in Fig. 1. Considering patients previously uncontrolled on OAD(s), in the Indian subpopulation of DUAL I extension, IDegLira resulted in a statistically significantly greater HbA_{1c} reduction versus IDeg [estimated treatment difference (ETD) −0.91%; 95% confidence interval (CI) −1.21 to −0.61 (−10 mmol/mol; 95% CI −13 to −7); $p < 0.0001$] and versus Lira [ETD −0.77%; 95% CI −1.08 to −0.46 (−8 mmol/mol; 95% CI −12 to −5); $p < 0.0001$]. In DUAL IV, a significantly greater reduction was observed with IDegLira versus placebo [ETD: −0.78%; 95% CI −1.25 to −0.31 (−9 mmol/mol; 95% CI −14 to −3); $p = 0.002$] in the Indian subpopulation. In patients previously uncontrolled on basal insulin (DUAL II), IDegLira also resulted in a greater HbA_{1c} reduction versus IDeg [maximum dose 50 U; ETD −1.32%; 95% CI −1.80 to −0.85 (−14 mmol/mol; 95% CI −20 to −9); $p < 0.0001$] in the Indian subpopulation.

The proportion of participants in the global study populations and the Indian subpopulations achieving HbA_{1c} <7% (<53 mmol/mol) are shown in Fig. 2. In the Indian subpopulation of the DUAL I extension trial, participants were significantly more likely to achieve an HbA_{1c} of <7% (<53 mmol/mol) with IDegLira than with IDeg [84.0 vs. 43.1%; odds ratio (OR) 6.77; 95% CI 3.35–13.65; $p < 0.0001$] or with Lira (84.0 vs. 47.5%; OR 5.84; 95% CI 2.86–11.90; $p < 0.0001$). Participants were also more likely to achieve an HbA_{1c} of <7% (<53 mmol/mol) with IDegLira than with placebo in the DUAL IV trial (69.6 vs. 16.7%; OR 11.47; 95% CI 2.79–47.17; $p < 0.001$). In DUAL II, participants were also more likely to achieve an HbA_{1c} of <7% (53 mmol/mol) with IDegLira versus IDeg (65.6 vs. 21.9%; OR 7.36; 95% CI 2.31–23.50; $p < 0.0007$).

Table 1 Baseline characteristics of overall and Indian subpopulations in the DUAL I extension, DUAL II and DUAL IV trials (full analysis set)

Baseline characteristics	Uncontrolled on OAD(s)										Uncontrolled on basal insulin			
	DUAL I extension						DUAL IV				DUAL II			
	Global trial population			Indian subpopulation			Global trial population		Indian subpopulation		Global trial population		Indian subpopulation	
	IDegLira	IDeg	Lira	IDegLira	IDeg	Lira	IDegLira	Placebo	IDegLira	Placebo	IDegLira	IDeg	IDegLira	IDeg
Number of people (n)	833	413	414	125	65	61	289	146	46	18	199	199	32	32
Age (years)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)	51.7 (10.0)	50.9 (9.0)	51.1 (8.1)	60.0 (9.6)	59.4 (10.8)	53.2 (7.9)	49.1 (8.8)	57 (9)	58 (11)	54.2 (8.9)	51.0 (9.5)
Male sex, n (%)	435 (52.2%)	200 (48.4%)	208 (50.2%)	68 (54.4%)	33 (50.8%)	37 (60.7%)	(53.3%)	(50.0%)	21 (45.7%)	6 (33.3%)	(56%)	(53%)	17 (53.1%)	15 (46.9%)
Body weight (kg)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)	69.1 (13.7)	73.8 (16.7)	72.6 (13.0)	87.2 (18.6)	89.3 (17.5)	68.0 (11.4)	68.4 (9.9)	95.4 (19)	93.5 (20)	78.5 (13.8)	81.7 (12.0)
BMI (kg/m^2)	31.2 (5.2)	31.2 (5.3)	31.3 (4.8)	26.9 (4.9)	28.7 (5.4)	27.9 (4.6)	31.2 (4.8)	32.0 (4.5)	27.1 (3.7)	28.6 (3.4)	33.6 (6)	33.8 (6)	30.8 (4.6)	32.3 (4.5)
Duration of diabetes (years)	6.6 (5.1)	7.0 (5.3)	7.2 (6.1)	5.62 (4.89)	4.93 (4.37)	5.72 (4.74)[a]	9.0 (5.5)	9.3 (6.5)	6.33 (4.71)	5.05 (3.69)	10 (6)	11 (7)	10.24 (4.16)	9.32 (5.85)
HbA$_{1c}$														
%	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)	8.3 (0.9)	8.6 (1.0)	8.3 (1.0)	7.9 (0.6)	7.9 (0.6)	8.0 (0.5)	8.1 (0.7)	8.7 (0.7)	8.8 (0.7)	9.0 (0.7)	9.1 (0.7)
mmol/mol	67 (10)	67 (11)	67 (10)	67 (10)	71 (11)	67 (11)	63 (7)	63 (7)	64 (5)	65 (8)	71 (8)	73 (8)	75 (8)	76 (8)
FPG (mmol/L)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)	8.6 (2.1)	8.9 (2.5)	8.8 (2.9)[a]	9.1 (2.2)	9.1 (2.1)	8.1 (2.1)	7.8 (1.7)	9.7 (2.9)	9.6 (3.1)	8.9 (2.4)	8.9 (2.5)
OAD at screening, n (%)														
Metformin	691 (83.0%)	343 (83.1%)	338 (81.6%)	88 (70.4%)	42 (64.6%)	37 (60.7%)								
Metformin + pioglitazone	142 (17.0%)	70 (16.9%)	75 (18.1%)	37 (29.6%)	23 (35.4%)	24 (39.3%)								
Metformin + SU							259 (89.6%)	129 (88.4%)	45 (97.8%)	16 (88.9%)	104 (52%)	101 (51%)	28 (87.5%)	27 (84.4%)
SU							30 (10.4%)	17 (11.6%)	1 (2.2%)	2 (11.1%)	95 (48%)	98 (49%)	4 (12.5%)	5 (15.6%)

See Gough et al. [8], Rodbard et al. [9] and Buse et al. [11] for more detail on these trials

Values in table are presented as the mean with the standard deviation (SD) in parenthesis unless indicated otherwise

BMI Body mass index, FPG fasting plasma glucose, HbA1c glycated hemoglobin, IDeg insulin degludec, IDegLira insulin degludec/liraglutide, Lira liraglutide, No. number, OAD oral antidiabetic drug, SU sulfonylurea

[a] Data available for n = 60 participants for these parameters
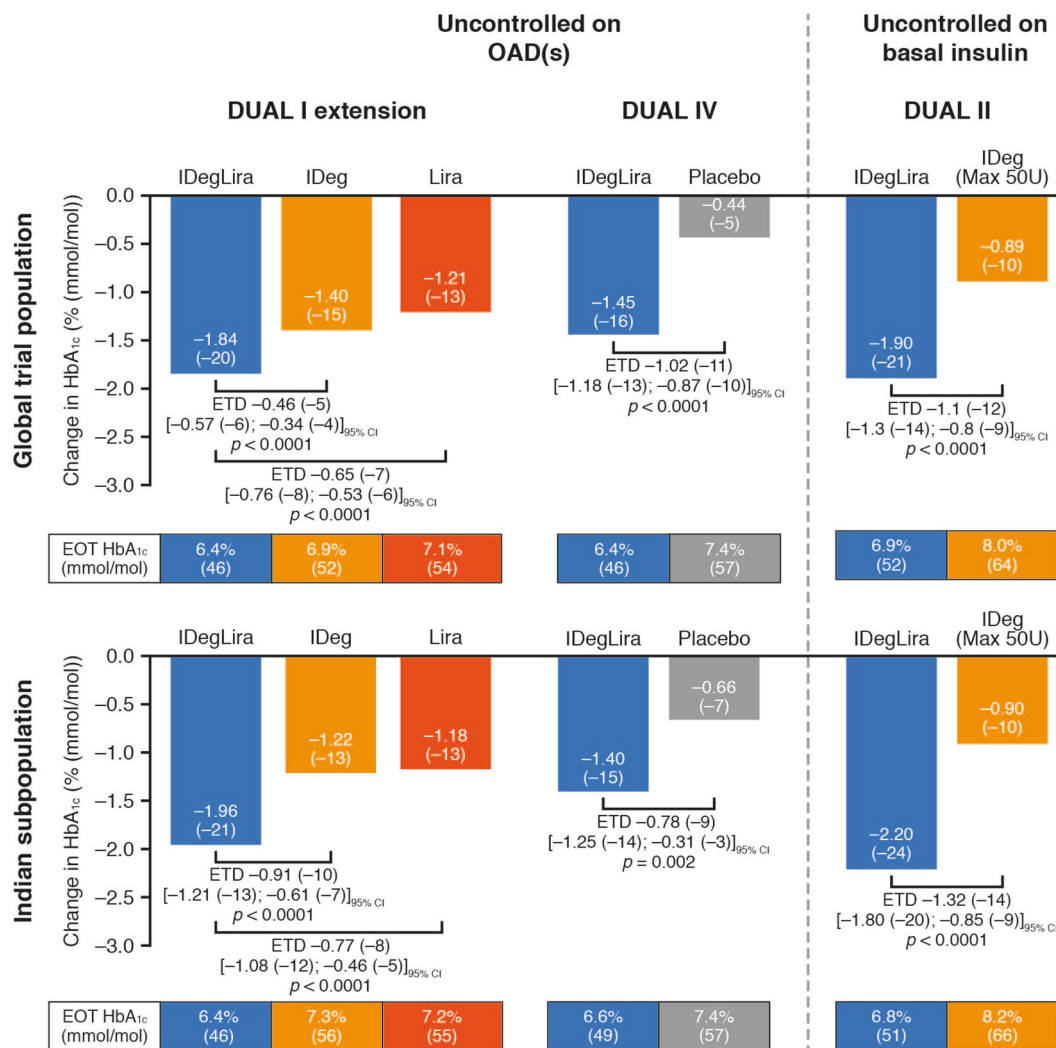
Fig. 1 Mean change in glycated hemoglobin (HbA$_{1c}$) and end-of-trial HbA$_{1c}$ in the global study population and the Indian subpopulations of the DUAL I extension, DUAL IV and DUAL II trials (maximum 50 U) [8, 9, 11, 12]. Mean observed values are based on full analysis set and data inputted using the last observation carried forward (LOCF) method. Treatment difference is estimated from an analysis of covariance (ANCOVA) analysis. *CI* Confidence interval *EOT* end of trial, *ETD* estimated treatment difference, *IDeg* insulin degludec, *IDegLira* insulin degludec/liraglutide, *Lira* liraglutide, *OAD* oral antidiabetic drug

In the DUAL I extension trial, IDegLira resulted in a greater FPG reduction versus Lira (ETD −29.80 mg/dL; 95% CI −39.62 to −19.98; $p < 0.0001$); differences versus IDeg were not statistically significant [TD −7.04 mg/dL; 95% CI −16.57 to 2.50; $p =$ not significant (ns)]. Differences versus placebo in the DUAL IV trial were also not statistically significant (ETD −18.65 mg/dL; 95% CI −38.80 to 1.50; $p =$ ns). IDegLira resulted in a greater FPG reduction versus IDeg (maximum dose 50 U) in DUAL II

(ETD −34.26 mg/dL; 95% CI −53.28 to −15.24; $p = 0.0006$).

Body Weight

In the Indian subpopulation of the DUAL I extension trial, IDegLira was weight neutral (−0.3 kg), whereas body weight increased with IDeg (1.8 kg; ETD −1.61 kg; 95% CI −2.45 to −0.78; $p = 0.0002$) and decreased with Lira
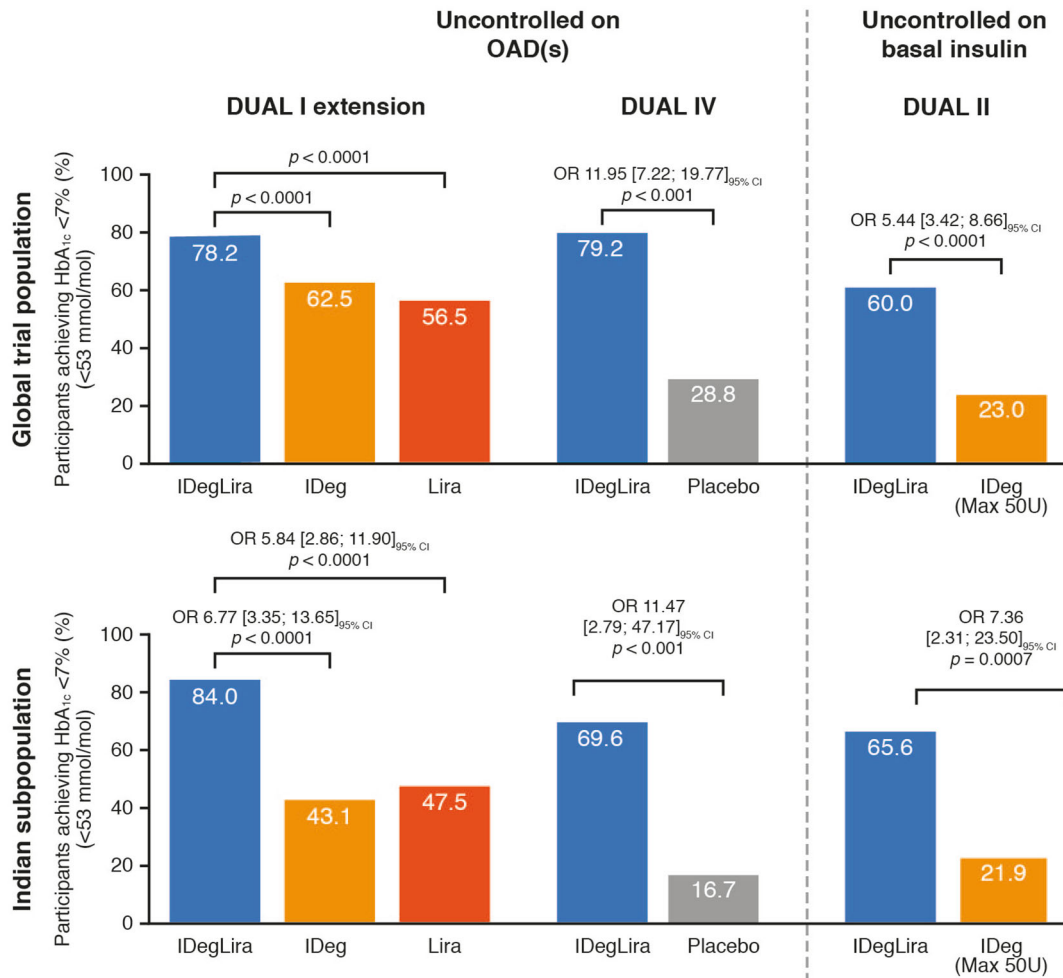
Fig. 2 Percentages of participants achieving the HbA$_{1c}$ target of <7% in the global study population and the Indian subpopulations of the DUAL I extension, DUAL IV and DUAL II trials (maximum 50 U) [8, 9, 11, 12].

Mean observed values are based on the full analysis set and LOCF inputted data. The odds ratio (*OR*) is estimated from a logistic regression analysis

(−2.3 kg; ETD 1.72 kg; 95% CI 0.87–2.58; $p < 0.0001$) (Fig. 3). In DUAL IV, the mean weight change was 0.6 kg with IDegLira and −0.9 kg with placebo (ETD 1.37 kg; 95% CI 0.31–2.43; $p = 0.0124$). IDegLira resulted in a greater weight loss versus IDeg (ETD −1.91 kg; 95% CI −3.39 to −0.43; $p = 0.01223$) in DUAL II. Across the studies, baseline body weights were lower in the Indian subpopulations.

Insulin Dose

End-of-trial insulin dose was 35 U with IDegLira and 59 U with IDeg in the DUAL I extension

trial, 25 U with IDegLira in the DUAL IV trial and 42 and 46 U with IDegLira and IDeg in the DUAL II trial.

Safety Endpoints

Adverse events for the global populations and Indian subpopulations are summarized in Table 2. Rates of gastrointestinal AEs (combined diarrhea, nausea and vomiting) were 25.3 events per 100 patient-years of exposure (PYE) in the IDegLira group, 8.5 per 100 PYE in the IDeg group and 75.3 per 100 PYE in the Lira-treated group in the DUAL I extension trial, and
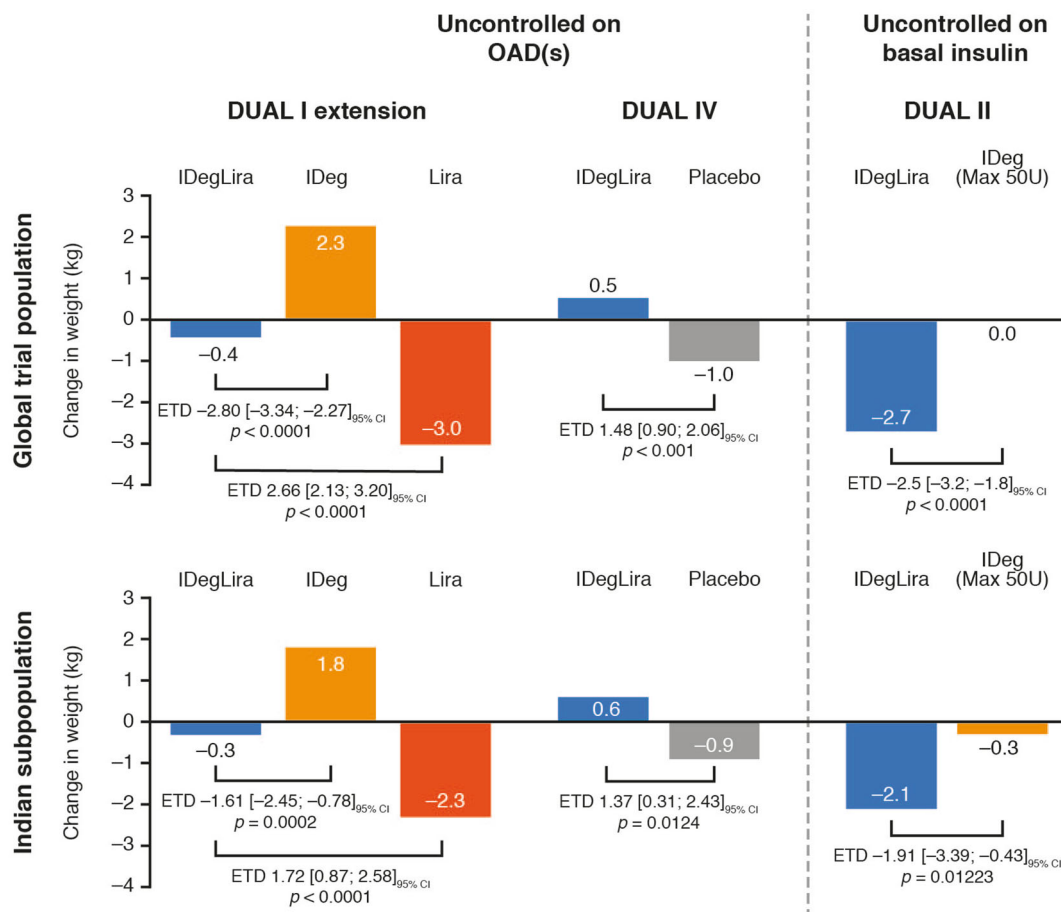
Fig. 3 Mean change in body weight in the global study population and Indian subpopulations of the DUAL I extension, DUAL II and DUAL IV trials [8, 9, 11]. Maximum dose of IDeg was 50 U in DUAL II. Mean observed values are based on full analysis set and LOCF inputted data. Treatment difference is estimated from an ANCOVA analysis

9.4 (IDegLira) and 36.2 (placebo) events/100 PYE in DUAL IV. In DUAL II, the rates were 82.1 (IDegLira) and 20.7 (IDeg) events/100 PYE.

There were no severe hypoglycemic episodes in the Indian subpopulations of the three trials. Confirmed hypoglycemia rates were 1.98, 1.08 and 0.37 events/PYE in the IDegLira, IDeg and Lira groups, respectively, in the DUAL I extension trial (compared with 1.77, 2.79 and 0.19 events/PYE in the global trial population) and 4.06 and 0.36 events/PYE with IDegLira and placebo, respectively, in DUAL IV (compared with 3.52 and 1.35 events/PYE in the global trial population). In DUAL II, confirmed hypoglycemia rates were 1.16 and 0.83 events/PYE with IDegLira and IDeg, respectively (compared with 1.53 and 2.63 events/PYE in the global trial population).

DISCUSSION

In the Indian subpopulations, IDegLira resulted in substantial HbA$_{1c}$ reductions that were significantly greater than those achieved by all comparators. Mean end-of-trial HbA$_{1c}$ with IDegLira was <7% (<53 mmol/mol) in all trials and more participants achieved a HbA$_{1c}$ target of <7% (<53 mmol/mol) versus all comparators, consistent with the global trial populations [8, 9, 11].

Table 2 Adverse events reported in the DUAL I extension, DUAL II and DUAL IV trials (full analysis set)

Adverse events	Uncontrolled on OAD(s)					Uncontrolled on basal insulin	
	DUAL I extension			DUAL IV		DUAL II	
	IDegLira	IDeg	Lira	IDegLira	Placebo	IDegLira	IDeg
Global trial population							
Number of exposed participants	825	412	412	288	146	199	199
Percentage of participants with AEs	71.2	70.6	77.2	N/A[a]	N/A[a]	57.8	61.3
AE rate per 100 PYE	407.9	383.3	507.3	401.4	367.0	398.1	355.5
Percentage of participants with SAEs	4.6	5.3	5.8	N/A[a]	N/A[a]	3.5	5.5
SAE rate per 100 PYE	6.7	8.9	9.3	20.3	8.0	12.0	14.4
Indian subpopulation							
Number of exposed participants	125	65	60	45	18	32	32
Percentage of participants with AEs	76.8	76.9	93.3	80.0	61.1	81.3	87.5
AE rate per 100 PYE	364.1	332.1	543.3	363.4	349.5	766.5	577.0
Percentage of participants with SAEs	2.4	1.5	5.0	0.0	0.0	3.1	3.1
SAE rate per 100 PYE	3.6	1.7	6.8	0.0	0.0	6.8	13.8

See Gough et al. [8], Rodbard et al. [9] and Buse et al. [11] for more detail on these trials

Data are based on safety analysis set

AEs Adverse events, *N/A* not available, *PYE* patient-years of exposure, *SAEs* serious adverse events

[a] Data for percentage of participants with AEs in the entire trial population for DUAL IV have not been published to date

IDegLira was generally weight-neutral when used as an add-on to oral therapy (DUAL I extension/DUAL IV) and resulted in weight loss when used after basal insulin (DUAL II).

Considering IDegLira alone, rates of confirmed hypoglycemia were consistent with those observed with IDegLira in the global trial populations. However, the rate of confirmed hypoglycemia with IDeg was substantially lower in the Indian subpopulations (by around 1.7/1.8 events/PYE) versus the global trial populations of DUAL I and II. As a result, the rate of confirmed hypoglycemia was numerically lower with IDeg versus IDegLira in the Indian subpopulations of DUAL I and II, while in the global trial population IDegLira resulted in a lower rate of hypoglycemia versus IDeg, reaching statistical significance in the DUAL I trial [8, 9]. This difference might be explained by the small number of participants—and therefore hypoglycemic events—in the Indian

subpopulations and by baseline differences. The hypoglycemia rates should also be considered in the context of the significantly lower mean end-of-trial HbA$_{1c}$ achieved with IDegLira compared to comparators.

IDegLira was generally well tolerated, with a lower rate of gastrointestinal AEs in the Indian subpopulation versus the global trial populations in DUAL I and IV, and a higher rate in DUAL II. Across all trials, the proportion of participants experiencing AEs was higher in the Indian subpopulation than in the global trial population, but the pattern of AEs did not differ [8, 9, 11].

An inherent limitation of this study is that it is a post hoc analysis of three randomized controlled DUAL trials that were not designed to compare the safety and efficacy of IDegLira in the Indian subpopulation versus the global population. As such, there were differences at baseline in terms of FPG and BMI with the

Indian subpopulation compared with the global population. Furthermore, owing to trial design differences, individual trial data were analyzed separately rather than the IDegLira data being pooled, and therefore sample sizes were small. Differences between Indian and non-Indian populations were not analyzed as the Indian population constituted a relatively low proportion of the global population.

CONCLUSION

In conclusion, results from the Indian subpopulations largely reflected those of the global study populations. These results provide evidence to support the efficacy and safety of IDegLira as a treatment modality for participants with type 2 diabetes uncontrolled on OADs and/or basal insulin of the South Asian population, offering better glucose control than either component alone, improved weight profile versus the basal insulin component, and with fewer gastrointestinal side effects than a GLP-1 analogue.

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