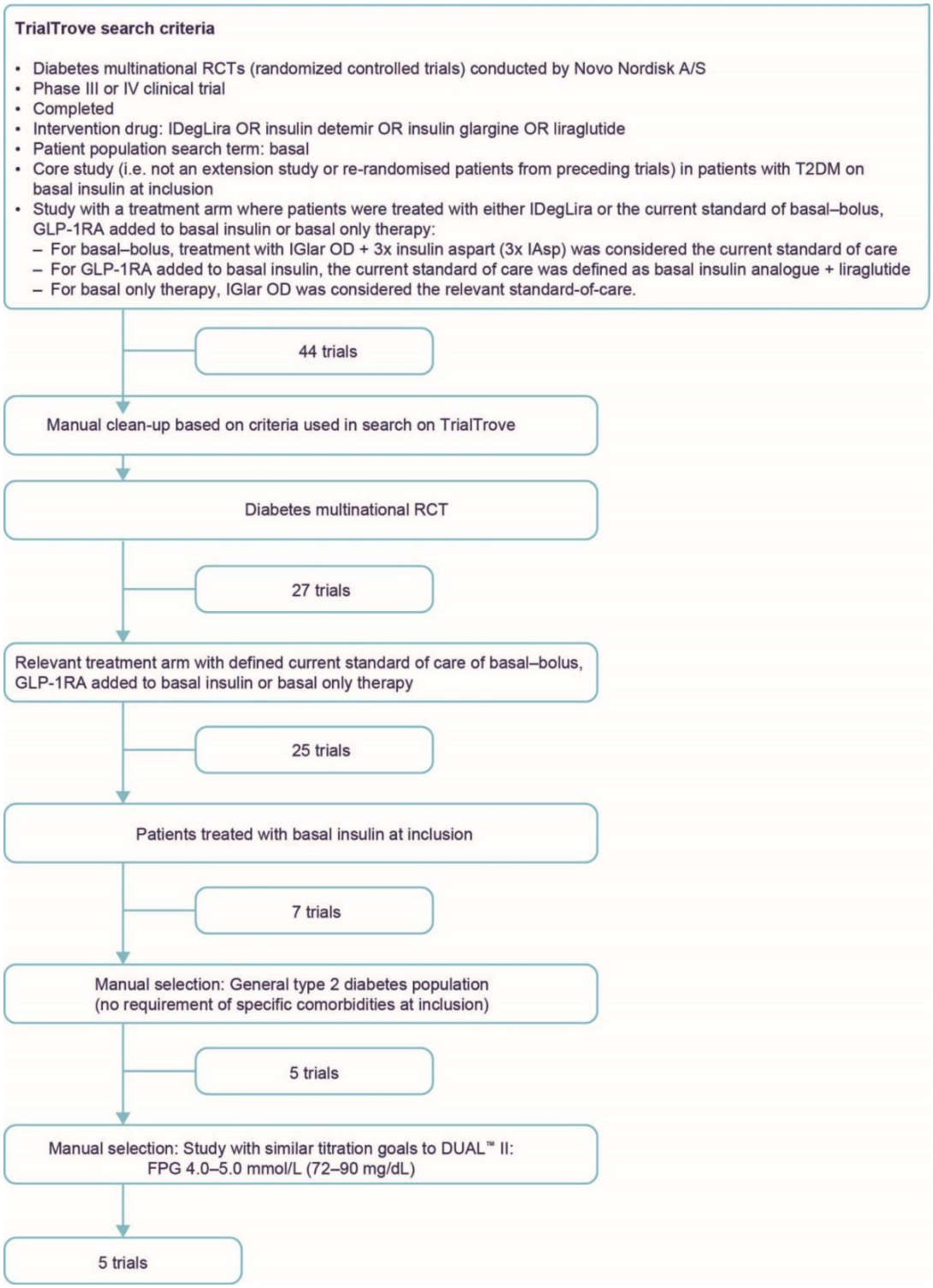
SUPPLEMENTARY MATERIAL

Figure S1. Search strategy for identifying relevant trials.



FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; IAsp, insulin aspart; IDegLira, insulin degludec/liraglutide; IGlar, insulin glargine; OD, once daily; T2DM, type 2 diabetes mellitus

Table S1. The DUAL™ development programme for IDegLira (July 2015) [S1–S6].

Trial name and registration number	Comparators/description	Duration	Status
DUAL I NCT01336023	IDegLira vs. IDeg and vs. Lira added on to OAD	26 weeks	Published in full Gough et al, 2014 [S1]
DUAL I extension NCT01336023	Extension of DUAL I	52 weeks	Published in full Gough et al, 2015 [S2]
DUAL II NCT01392573	IDegLira vs. IDeg in patients previously treated with basal insulin	26 weeks	Published in full Buse et al, 2014 [S3]
DUAL III NCT01676116	Switch to IDegLira from (daily) GLP-1 receptor agonist therapy vs. unchanged GLP-1RA therapy	26 weeks	Published as abstract Linjawi et al, 2015 [S4]
DUAL IV NCT01618162	IDegLira add-on to SU vs. placebo	26 weeks	Published as abstract Rodbard et al, 2015 [S5]
DUAL V NCT01952145	Basal insulin optimization vs. IGlar	26 weeks	Published as abstract Buse et al, 2015 [S6]
DUAL V extension NCT02100475	Extension of DUAL V	52 weeks	Ongoing
DUAL VI NCT02298192	Comparison of once-weekly vs. twice-weekly titration of IDegLira	32 weeks	Ongoing
DUAL VII	IDegLira vs. full basal–bolus therapy (IGlar + IAsp)	26 weeks	In planning stages

GLP-1, glucagon-like peptide-1; IAsp, insulin aspart; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide; IGlar, insulin glargine; Lira, liraglutide; OAD, oral antidiabetic drug; SU, sulfonylurea.

Supplemental references:

S1. Gough S, 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;2:885–93.

S2. Gough S, Bode B, Woo V, 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: doi: 10.1111/dom.12498.

S3. Buse JB, Vilsbøll T, Thurman J, et al; NN9068-3912 (DUAL-II) Trial Investigators. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Care 2014;37:2926–33.

S4. Linjawi S, Bode B, Chaykin L, et al. Efficacy and safety of IDegLira (combination of insulin degludec + liraglutide), in insulin naïve patients with T2D uncontrolled on GLP-1 receptor agonist (GLP-1RA) therapy. Diabetes. 2015;64(Suppl. 1):A255 (Abstract 1002-P).

S5. Rodbard H, Bode B, Harris S, et al. IDegLira in insulin-naïve patients with type 2 diabetes (T2D) inadequately controlled on sulfonylureas (SU) alone or in combination with metformin: The DUAL IV Study. Diabetes. 2015;64(Suppl. 1):A255 (Abstract 1003-P).

S6. Buse J, Pérez Manghi P, Garcia-Hernandez P, et al. Insulin degludec/liraglutide (IDegLira) is superior to insulin glargine (IG) in A1c reduction, risk of hypoglycemia and weight change: DUAL V Study. Diabetes. 2015;64(Suppl. 1):A43 (Abstract 166-OR).

Table S2. Results from the supplementary analysis: 4-arm model with 210 patients in the basal–bolus arm.

(a) Estimated end-of-treatment HbA_{1c} values, changes from baseline to end-of-treatment per treatment arm, and daily basal insulin dose at end-of-treatment, based on ANCOVA model.

	IDegLira (N = 199)		GLP-1RA add-on to basal insulin (N = 225)		Basal–bolus with insulin glargine or insulin degludec as basal component (N = 210)		Basal only (up-titrated insulin glargine) (N = 329)	
	Mean (SD)	**95% CI**	**Mean (SD)**	**95% CI**	**Mean (SD)**	**95% CI**	**Mean (SD)**	**95% CI**
EOT HbA_{1c}, %	6.75 (0.96)	[6.61; 6.89]	7.09 (0.96)	[6.94; 7.24]	7.08 (0.96)	[6.94; 7.22]	7.38 (0.96)	[7.27; 7.48]
Δ HbA_{1c}, %	–1.66 (0.96)	[–1.80; –1.51]	–1.32** (0.96)	[–1.47; –1.17]	–1.33**(0.96)	[–1.47; –1.19]	–1.03** (0.96)	[–1.14; –0.92]
Δ HbA_{1c}, mmol/mol[a]	–18 (12)	[–20; –17]	–14** (12)	[–16; -13]	–14** (11)	[–16; –13]	–11** (11)	[–12; –10]
Δ Body weight, kg	–2.95(3.78)	[–3.50; –2.39]	–3.57 (3.78)	[–4.16; –2.98]	3.91** (3.78)	[3.36; 4.47]	1.20** (3.78)	[0.77; 1.62]
Δ BMI (kg/m^2)	–1.04 (1.34)	[–1.23; –0.84]	–1.29 (1.34)	[–1.49; –1.08]	1.38** (1.34)	[1.19; 1.58]	0.43** (1.34)	[0.28; 0.58]
Δ SBP (mmHg)	–6.86 (13.20)	[–8.80; –4.92]	–4.67 (13.20)	[–6.72; –2.63]	0.93**(13.20)	[–2.85; 1.00]	–3.49** (13.20)	[–4.97; –2.01]
Δ total cholesterol (mg/dL)	–10.13(30.28)	[–14.59; –5.67]	–12.66 (30.28)	[–17.37; –7.95]	1.50** (30.28)	[–2.94; 5.94]	–2.65** (30.28)	[–6.06; 0.77]
Δ LDL cholesterol (mg/dL)	–6.85 (23.83)	[–10.36; –3.34]	–9.07 (23.83)	[–12.79; –5.35]	0.076** (23.83)	[–3.43; 3.58]	–2.65 (23.83)	[–5.33; 0.04]
Δ HDL cholesterol (mg/dL)	0.52 (6.79)	[–0.48; 1.52]	–0.77 (6.79)	[–1.83; 0.29]	0.79 (6.79)	[–0.21; 1.78]	1.10 (6.79)	[0.33; 1.86]
Δ triglycerides (mg/dL)	–25.74 (103.71)	[–41.01; –10.47]	–18.99 (103.71)	[–35.13; –2.86]	3.82** (103.71)	[–11.39; 19.03]	–3.05* (103.71)	[–14.82; 8.72]
EOT daily basal dose [U]	37.27 (30.22)[b]	[32.82; 41.71]	35.89 (30.22)[c]	[31.24; 40.55]	68.22** (30.22)[d]	[63.80; 72.64]	61.58** (30.22)	[58.17; 64.99]

Δ, change from baseline; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; EOT, end-of-treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; IDegLira, insulin degludec/liraglutide; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

IDegLira significantly different: *$P < 0.05$, **$P < 0.01$ (for exact values see Table 4b). Reported SDs are model based.

[a] Calculated values; [b] Daily GLP-1RA dose at end-of-treatment was 1.34 mg (one dose step of IDegLira = 1 U insulin degludec + 0.036 mg liraglutide); [c] Daily GLP-1RA dose at end-of-treatment was 1.8 mg; [d] Daily bolus dose at end-of-treatment was 57.90 U. Basal/bolus split: 54.1%/45.9%.

(b) Estimated end-of-treatment differences for IDegLira versus comparators and daily basal insulin dose at end-of-treatment, based on ANCOVA model.

	IDegLira vs. GLP-1RA add-on to basal insulin (N = 199)			**IDegLira vs. basal–bolus with insulin glargine or insulin degludec as basal component (N = 210)**			**IDegLira vs. basal-only (up-titrated insulin glargine) (N = 329)**		
	Mean	**95% CI**	***P*-value**	**Mean**	**95% CI**	***P*-value**	**Mean**	**95% CI**	***P*-value**
Δ HbA_{1c}, %	–0.34	[–0.54; –0.13]	0.0013	–0.33	[–0.52; –0.13]	0.0009	–0.63	[–0.80; –0.45]	<0.0001
Δ HbA_{1c}, mmol/mol [a]	–4	[–6; –1]	0.0013	–4	[–6; –1]	0.0009	–7	[–9; –5]	<0.0001
Δ Body weight, kg	0.63	[–0.18; 1.44]	0.1293	–6.86	[–7.62; –6.09]	<0.0001	–4.14	[–4.84; –3.44]	<0.0001
Δ BMI (kg/m2)	0.25	[–0.04; 0.54]	0.0855	–2.42	[–2.69; –2.15]	<0.0001	–1.47	[–1.72; –1.22]	<0.0001
Δ SBP (mmHg)	–2.19	[–5.02; 0.64]	0.1291	–5.94	[–8.61; –3.26]	<0.0001	–3.37	[–5.82; –0.91]	0.0072
Δ total cholesterol (mg/dL)	2.53	[–3.97; 9.02]	0.4453	–11.63	[–17.79; –5.48]	0.0002	–7.48	[–13.15; –1.82]	0.0096
Δ LDL cholesterol (mg/dL)	2.22	[–2.90; 7.34]	0.3956	–6.93	[–11.78; –2.08]	0.0052	–4.21	[–8.65; 0.24]	0.0638
Δ HDL cholesterol (mg/dL)	1.29	[–0.17; 2.75]	0.0834	–0.26	[–1.64; 1.11]	0.7075	–0.58	[–1.84; 0.69]	0.3727
Δ Triglycerides (mg/dL)	–6.75	[–29.00; 15.50]	0.5519	–29.56	[–50.59; –8.53]	0.0059	–22.69	[–42.14; –3.24]	0.0222
EOT daily basal dose [U]	1.37	[–5.08; 7.82]	0.6767	–30.95	[–37.08; –24.83]	<0.0001	–24.32	[–29.95; –18.68]	<0.0001

Δ, change from baseline; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; EOT, end-of-treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; IDegLira, insulin degludec/liraglutide; LDL, low-density lipoprotein; SBP, systolic blood pressure.

[a] Calculated values.

Table S3. Observed outcomes/changes from baseline in each of the treatment arms contributing to the pooled analysis and supplementary analysis.

	IDegLira (N = 199)	**Liraglutide 1.8 mg added to basal insulin (N = 225)**	**Basal–bolus with insulin glargine as basal component (N = 56)**	**Basal–bolus with insulin glargine or insulin degludec as basal component (N = 210)**	**Up-titrated insulin glargine (N = 329)**
EOT HbA_{1c} (%)	6.85 (0.99)	6.95 (1.02)	7.04 (1.38)	7.02 (1.18)	7.37 (0.98)
Δ HbA_{1c} (%)	–1.90 (1.09)	–1.25 (1.00)	–1.43 (1.14)	–1.34 (1.18)	–0.99 (1.02)
Δ HbA_{1c} (mmol/mol) [a]	–21 (12)	–14 (11)	–16 (12)	–15 (13)	–11 (11)
Δ Weight (kg)	–2.68 (3.68)	–3.29 (3.55)	+4.24 (4.79)	+4.08 (5.23)	+1.04 (3.03)
Δ BMI (kg/m^2)	–0.94 (1.29)	–1.20 (1.24)	+1.51 (1.71)	+1.44 (1.86)	+0.38 (1.10)
Δ SBP (mmHg)	–5.40 (14.11)	–5.40 (14.40)	+3.29 (13.98)	–0.05 (16.56)	–3.36 (15.52)
Δ Total cholesterol (mg/dL)	–11.79 (33.54)	–12.35 (36.12)	–2.68 (35.65)	+3.66 (34.32)	–1.44 (28.17)
Δ HDL cholesterol (mg/dL)	+1.36 (6.91)	–1.80 (7.94)	+1.21 (6.34)	+1.53 (7.06)	+1.51 (7.08)
Δ LDL cholesterol (mg/dL)	–8.62 (27.22)	–8.61 (25.73)	–1.30 (31.13)	+1.71 (27.21)	–2.90 (25.21)
Δ Triglycerides (mg/dL)	–29.47 (140.32)	–13.48 (82.74)	–14.32 (78.31)	+2.09 (138.60)	+0.96 (60.17)
EOT daily basal insulin (U)	44.82 (9.41)	43.19 (31.11)	67.65 (42.46)	71.69 (47.28)	56.88 (34.34)
EOT daily bolus insulin (U)	–	–	58.09[b]	60.82[c]	–
Overall confirmed hypoglycemia (events/100 PYE)	153	126	1539	1072	340
Severe hypoglycemia event rate (events/100 PYE)	1	0	4	4	4
Non-severe hypoglycemia event rate (events/100 PYE)	152	126	1535	1068	336

Δ , change from baseline; BMI, body mass index; EOT, end-of-treatment; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; IDegLira, insulin degludec/liraglutide; LDL, low-density lipoprotein; PYE, patient-year of exposure; SBP, systolic blood pressure.

[a] Calculated values; [b] Basal/bolus split as % at end of treatment: 53.8/46.2; [c] Basal/bolus split as % at end of treatment: 54.1/45.9.

Table S4. Results from the supplementary analysis: 4-arm model with 210 patients in the basal–bolus arm.

(a) Estimated rates of confirmed hypoglycemia for IDegLira versus comparators, based on a negative binomial model.

	IDegLira (N = 199)		GLP-1RA add-on to basal insulin (N = 225)		Basal–bolus with insulin glargine or insulin degludec as basal component (N = 210)		Basal oral (up-titrated insulin glargine) (N = 329)	
	Events/ 100 PYE	**95% CI**	**Events/ 100 PYE**	**95% CI**	**Events/ 100 PYE**	**95% CI**	**Events/ 100 PYE**	**95% CI**
Overall confirmed hypoglycemia	125.9	[95.45; 166.11]	124.7	[92.74; 167.59]	797.9**	[637.47; 998.68]	289.0**	[238.40; 350.24]
Severe hypoglycemia	0.8	[0.10; 6.71]	NA	NA	2.9	[1.01; 8.02]	3.5	[1.41; 8.82]
Non-severe hypoglycemia	125.1	[94.68; 165.15]	124.5	[92.52; 167.44]	794.6**	[634.32; 995.44]	285.5 **	[235.31; 346.46]

CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide; PYE, patient-year of exposure.

IDegLira significantly different: ** $P < 0.01$.
NA, not applicable: could not be estimated as no severe hypoglycemic events were observed with GLP-1RA add-on to basal insulin.
Confirmed hypoglycemia was defined as the occurrence of severe episodes (i.e. requiring assistance), or episodes in which plasma glucose concentration (confirmed by self-monitored blood glucose) was less than 3.1 mmol/L (56 mg/dL), irrespective of symptoms.

(b) Estimated rate ratios for confirmed hypoglycemia, based on a negative binomial model.

	IDegLira vs. GLP-1RA add-on to basal insulin			IDegLira vs. basal–bolus with insulin glargine or insulin detemir as basal component			IDegLira. vs. basal-only (up-titrated insulin glargine)		
	Rate ratio	**95% CI**	***P*-value**	**Rate ratio**	**95% CI**	***P*-value**	**Rate ratio**	**95% CI**	***P*-value**
Overall confirmed hypoglycemia	1.01	[0.68; 1.51]	0.96	0.16	[0.11; 0.22]	<0.0001	0.44	[0.31; 0.61]	<0.0001
Severe hypoglycemia	NA	NA	NA	0.29	[0.03; 2.72]	0.28	0.24	[0.03; 2.21]	0.21
Non-severe hypoglycemia	1.00	[0.67; 1.50]	0.98	0.16	[0.11; 0.22]	<0.0001	0.44	[0.31; 0.61]	<0.0001

CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide.
NA, not applicable: could not be estimated as no severe hypoglycemic events were observed with GLP-1RA add-on to basal insulin.

Table S5. Results from the supplementary analysis: 4-arm model with 210 patients in the basal–bolus arm.
(a) Estimated responder rates per treatment arm, based on a logistic regression model.

	IDegLira (N = 199)	**GLP-1RA add-on to basal insulin (N = 225)**	**Basal–bolus (N = 210)**	**Basal only (glargine or degludec) (N = 329)**
Δ HbA_{1c} in all subjects, %	–1.66	–1.32	–1.33	–1.03
Δ HbA_{1c} in all subjects, mmol/mol	–18	–14	–14	–11
HbA_{1c} <7.0% (53 mmol/mol)	64.5%	46.9%	52.8%	32.5%
HbA_{1c} <7.0% without hypoglycemia	45.0%	35.0%	5.40%	16.0%
HbA_{1c} <7.0% without hypoglycemia and no weight gain	39.3%	32.9%	0.9%	7.7%

Δ, change from baseline; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; IDegLira, insulin degludec/liraglutide. Rates are shown as percentage of patients, except for HbA_{1c} changes.

(b) Estimated odds ratios for responder rates for IDegLira versus comparators in all subjects, based on a logistic regression model.

	IDegLira vs. GLP-1RA add-on to basal insulin			**IDegLira vs. basal–bolus with insulin glargine as basal component**			**IDegLira. vs. basal-only (up-titrated insulin glargine)**		
In all subjects	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**	**Odds ratio**	**95% CI**	***P*-value**
HbA_{1c} <7.0% (53 mmol/mol)	2.06	[1.30 ; 3.27]	0.0021	1.63	[1.05 ; 2.51]	0.028	3.78	[2.51 ; 5.71]	<0.0001
HbA_{1c} <7.0% without hypoglycemia	1.52	[0.95 ; 2.44]	0.084	14.26	[7.22 ; 28.13]	<0.0001	4.32	[2.75 ; 6.78]	<0.0001
HbA_{1c} <7.0% without hypoglycemia and no weight gain	1.32	[0.80 ; 2.20]	0.28	71.53	[16.88 ; 303.21]	<0.0001	7.78	[4.54 ; 13.33]	<0.0001

CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; IDegLira, insulin degludec/liraglutide.