Supplementary Table 1 Study characteristics

Study	Study design	Location	Patient population	Intervention	Comparator	Efficacy endpoint	Efficacy outcome time-point
Watada et al.[30]	Double-blind, multicenter, treat-to-target trial	Japan	Adults with type 2 diabetes	iDegLira	Degludec	Mean HbA1c changed from 8.61% at baseline by -1.95% with iDegLira, Mean HbA1c changed from 8.56% by -0.65%, estimated treatment difference was -1.28% points; 95%CI [-1.50 to -1.06] p<0.0001	26-weeks
Rodbard et al.[31]	randomized, double-blind, parallel-group trial	Bulgaria, Canada, Germany, India, Israel, Puerto Rico, Turkey, United States	Adults with type 2 diabetes	IDegLira	Placebo	The mean HbA1c decreased from 63 mmol/mol (7.9%) to 46 mmol/mol (6.4%) with IDegLira and to 57 mmol/mol (7.4%) with placebo [estimated treatment difference –11 mmol/mol (95% CI –13; –10) or –1.02% (95% CI –1.18; –0.87); P < 0.001]. The HbA1c target of 53 mmol/mol (<7%) was achieved by 79.2% of participants in the IDegLira group vs 28.8% in the placebo group [estimated odds ratio 11.95 (95% CI 7.22; 19.77); P < 0.001].	26-weeks
Kaku et al.[23]	open-label, randomised, three arm, parallel group	Japan	Adults with type 2 diabetes	iDeglira	Degludec	Mean HbA1c decreased from 8.52% to 6.10% with iDeglira; 8.53% to 6.73% with degludec; 8.32% to 6.52% with liraglutide; mean HbA1c was reduced to a greater degree with IDegLira versus liraglutide, -2.42% vs -1.80%, estimated treatment difference (ETD) -0.48% [95%CI -0.60;-0.37%, p<0.0001; mean HbA1c also significantly reduced with iDegLira compared with degludec -2.42% vs -1.80%, ETD -0.63% [95%CI -0.75%;-0.52%] p < 0.0001; superiority of IdegLira versus degludec (-0.63% [95%CI -0.75;-0.52]; p<0.0001	52-weeks
Philis-Tsimikas et al.[32]	open-label, parallel-group,	Argentina, Canada, Finland, Hungary, India, Russian Federation, Slovakia,	Adults with type 2 diabetes	Insulin degludec/ liraglutide	(IGlar U100)	Mean HbA1c reductions were 1.9%-points with IDegLira and 1.7%-points with IGlar U100; confirming non-inferiority (P < 0.0001) and superiority of IDegLira (difference in HbA1c change -3.90 mmol/mol; 95% confidence interval [CI] -5.45; -2.35 (-0.36%-points; 95% CI -0.50, -	26-week

	treat-to-target trial	Slovenia, Spain, Switzerland, United States		(IDegLira)		0.21)).	
Aroda et al.[33]	International, multicentre, open-label, randomised controlled trial	Argentina, Czech Republic, Hungary, India, Israel, Italy, Mexico, Norway, Poland, Russian Federation, Slovakia, South Africa, Turkey, United Kingdom, United states	Adults with type 2 diabetes	IDegLira	IGlar U100	DegLira (n=506) or IGlar U100 (n=506). 484 (96%) of 506 in the IDegLira group and 481 (95%) of 506 in the IGlar U100 group completed the trial. Baseline characteristics were similar and representative of patients eligible for basal insulin intensification (overall mean diabetes duration 10 years; HbA1c 8·5% [69 mmol/mol]; fasting plasma glucose 10 mmol/L). Patients in the IDegLira group had significantly longer time until intensification was needed than those in the IGlar U100 group (median >2 years vs about 1 year). Fewer patients in the IDegLira group needed treatment intensification over 104 weeks than those in the IGlar U100 group (189 [37%] of 506 vs 335 [66%] of 506). The preplanned sensitivity analyses of the primary endpoint were in agreement with the primary analysis (hazard ratio 0·45 [95% CI 0·38-0·54]) in the proportional hazards regression model and the generalised log-rank test was also in favour of IDegLira (p<0·0001).	104-weeks
Billings et al.[34]	multinational, open-label, two-arm parallel, randomized trial	Argentina, Czech Republic, France, Greece, Hungary, Israel, Mexico, Russian Federation, Slovakia, Spain, Turkey, United States	Adults with type 2 diabetes	IDegLira	IGlar U100 and insulin aspart ≤4 times per day.	Glycated hemoglobin (HbA1c) decreased from 8.2% (66 mmol/mol) to 6.7% (50 mmol/mol) with IDegLira and from 8.2% (67 mmol/mol) to 6.7% (50 mmol/mol) with basal-bolus (estimated treatment difference [ETD] -0.02% [95% CI -0.16, 0.12]; -0.2 mmol/mol [95% CI -1.7, 1.3]), confirming IDegLira noninferiority versus basal-bolus (*P* < 0.0001).	26-week
Harris et al.[35]	Open-label, randomized	Austria, Bulgaria, Canada, Czechia, Hungary, Russian Federation, Serbia, Slovakia, United States	Adults with type 2 diabetes	IDegLira (titrated once weekly)	IDegLira (titrated twice weekly)	Mean HbA1c decreased from 8.2% (65 mmol/mol) to 6.1% (43 mmol/mol) with once-weekly titration and from 8.1% (65 mmol/mol) to 6.0% (42 mmol/mol) with twice-weekly titration; non-inferiority was confirmed (estimated treatment difference: 0.12% [−0.04; 0.28]95% CI, 1.30 mmol/mol [−0.41; 3.01]95% CI). Approximately 90% of patients achieved HbA1c < 7% in each arm.	32-week
Rosenstock	randomised, open-	Chile, Czech Republic, Germany, Denmark,	Adults with type 2 diabetes	iGlarLixi	insulin glargine (U100)	mean HbA1c was reduced from 8.0% at baseline to 6.3% and 6.5% with LixiLan and Gla-100, respectively, establishing statistical	24-

et al.[26]	label, parallel group multicenter	France, Hungary, Lithuania, Mexico, Poland, Romania, Slovakia, Sweden, and the U.S.				noninferiority and superiority of LixiLan (least-squared mean [95% CI] difference: -0.17% [-0.31, -0.04] {-1.9 mmol/mol [-3.4, -0.4]}; P = 0.01).	weeks
Lingvay et al.[25]	multinational, multicenter, 26-week, randomized, open-label, 2-group, treat-to-target trial	Argentina, Australia, Greece, Hungary, Mexico, Russian Federation, Slovakia, South Africa, Spain, United States	Adults with type 2 diabetes	Insulin Degludec/ Liraglutide	Insulin Glargine	Baseline HbA1c level was 8.4% for the degludec/liraglutide group and 8.2% for the glargine group. HbA1c level reduction was greater with degludec/liraglutide vs glargine (-1.81% for the degludec/liraglutide group vs -1.13% for the glargine group; estimated treatment difference [ETD], -0.59% [95% CI, -0.74% to -0.45%]), meeting criteria for noninferiority (P < .001), and also meeting criteria for statistical superiority (P < .001).	26-weeks
Rosenstock et al.[28]	Randomized, parallel, open label, 3-arm-treatment	Australia, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Italy, Latvia, Lithuania, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, Sweden, Ukraine, United Kingdom, United States	Adults with type 2 diabetes	iGlarLixi	Insulin Glargine and lixisenatide	Greater reductions in HbA1c from baseline (8.1%) were achieved with iGlarLixi compared with iGlar and Lixi (-1.6%, -1.3%, -0.9%, respectively), reaching mean final HbA1c levels of 6.5% for iGlarLixi versus 6.8% and 7.3% for iGlar and Lixi, respectively (both P < 0.0001).	30-weeks
Gough et al.[36]	Randomised, Parallel Three-arm, Open-label,	Australia, Canada, Finland, Germany, Hungary, India, Ireland, Italy, Malaysia, Mexico, Russian Federation, Singapore, Slovakia,	Adults with type 2 diabetes	Fixed Ratio Combination of Insulin Degludec and Liraglutide	Insulin Degludec or Liraglutide Alone	mean HbA1c had decreased by 1·9% (SD 1·1) to 6·4% (1·0) with IDegLira, by 1·4% (1·0) to 6·9% (1·1) with insulin degludec, and by 1·3% (1·1) to 7·0% (1·2) with liraglutide. IDegLira was non-inferior to insulin degludec (estimated treatment difference -0·47%, 95% CI -0·58 to -0·36, p<0·0001) and superior to liraglutide (-0·64%, -0·75 to -0·53,	26-week

	Multi-centre, Multinational Treat-to-target Trial	South Africa, Spain, Taiwan, Thailand, United Kingdom and United States				p<0·0001).	
Gough et al.[37]	open label, extension study	Australia, Canada, Finland, Germany, Hungary, India, Ireland, Italy, Malaysia, Mexico, Russian Federation, Singapore, Slovakia, South Africa, Spain, Taiwan, Thailand, United Kingdom and United States	Adults with type 2 diabetes	insulin degludec/liraglutide	insulin glargine	Mean glycated haemoglobin (HbA1c) concentration at 52 weeks was reduced from baseline by 1.84% for the IDegLira group, 1.40% for the insulin degludec group and 1.21% for the liraglutide group.	26-week extension
Lixi-Lan G study (NCT02787551) not yet published	international, open label, extension study	Canada, Estonia, Germany, Israel, Italy, Romania, Slovakia, Spain, United States	Adults with type 2 diabetes	Insulin Glargine/Lixisenatide Fixed Ratio Combination	GLP-1 RA receptor agonist (liraglutide QD, exenatide BID, exenatide extended-release QW, albiglutide QW, or dulaglutide QW) injected subcutaneously QD for 26 weeks on top of OAD therapy. GLP-1 RAs were administered as per local labeling at the same dose schedule as prior to randomization.	iGlarLixi group on entry HbA1c for: 7.78 % (SD 0.62) and reduced by -1.02 (0.048) at EOT ; GLP-1 analogue HbA1c 7.80% (SD 0.56) and reduced by -0.38 (SD 0.048) at EOT	26-weeks with 26-week extension

NCT02911948- Not yet published	international, randomised, double blind	Japan	Adults with type 2 diabetes	IDegLira	insulin degludec	iDeglira entry 8.61% (SD 0.88) by - 1.95 (1.01) EoT; Placebo entry 8.56 (SD 0.80) by -0.65 (SD 0.98)	26-weeks

Supplementary Table 2 Study arm baseline characteristics

Author	ARMS	Baseline Characteristics																
		Gender	Ethnic Origin											OAD at screening				
		M(%)/F(%)	White	Black	Asian	Other	Age (years)	Bodyweight	BMI (kg/m^2)	Duration of Diabetes Years	(HbA_{1c} (%)	HbA_{1c} (mmol/mol)	FPG (mmol/L)	Metformin	Metformin plus Pioglitazone	Second Oral glucose-lowering agent	Sulphonylurea	Other
Gough et al.[36]	IDegLira (n=833)	52/48	62%	9%	27%	2.0%	55.1	87.2	31.2	6.6	8.3	67.0	9.2	83%	17%	N/A	N/A	N/A
	Insulin Degludec (n=413)	48/52	62%	6%	29%	3.0%	54.9	87.4	31.2	7.0	8.3	67.3	9.4	83%	17%	N/A	N/A	N/A
	Liraglutide (n=414)	50/50	62%	7%	28%	3.0%	55.0	87.4	31.3	7.2	8.3	66.8	9.0	82%	18%	N/A	N/A	N/A
Gough et al.[37]	IDegLira (n=833)	52/48	62%	9%	27%	2.0%	55.1	87.2	31.2	6.6	8.3	67	9.2	83%	17%	N/A	N/A	N/A
	Insulin Degludec (n=413)	48/52	62%	6%	29%	3.0%	54.9	87.4	31.2	7.0	8.3	67	9.4	83.1%	16.9%	N/A	N/A	N/A
	Liraglutide (n=414)	50/50	62%	7%	28%	3.0%	55.0	87.4	31.3	7.2	8.3	67	9.0	81.6%	18.1%	N/A	N/A	N/A
Rosenstock et al.[28]	iGlarLixi (n=469)	47.3/52.7	88.9%	7.0%	1.7%	2.3%	58.2	N/A	31.6	8.9	8.1	65	9.9	Yes	N/A	58.4	55.2	(b), (c), (d)
	iGlar (n= 467)	50.7/49.3	90.1%	7.1%	1.5%	1.3%	58.3	N/A	31.7	8.7	8.1	65	9.8	Yes	N/A	57.8	53.3	(b), (c), (d)
	Lixi (n=234)	56.8/43.2	92.3%	5.1%	1.3%	1.3%	58.7	N/A	32.0	8.9	8.1	65	9.8	Yes	N/A	56.8	52.6	(b), (c), (d)
	All (n=1170)	50.6/49.4	90.1%	6.7%	1.5%	1.7%	58.4	N/A	31.7	8.8	8.1	65	9.8	Yes	N/A	57.9	53.9	(b), (c), (d)
Lingvay et al.[25]	Degludec/Liraglutide (n=278)	51.4/48.6	94.2%	2.2%	3.2%	0.4%	58.4	88.3	31.7	11.64	8.4	N/A	8.9	N/A	N/A	N/A	N/A	N/A
	Glargine (n=279)	49.1/50.9	95.0%	1.8%	3.2%	0.0%	59.1	87.3	31.7	11.33	8.2	N/A	8.9	N/A	N/A	N/A	N/A	N/A
Rosenstock et al.[26]	LixiLan (n=161)	49.7/50.3	98.1	N/A	N/A	N/A	56.9	90.1	32.2	6.3	8.1	64	9.8	Yes	N/A	N/A	N/A	N/A
	Gla-100 (n+162)	52.5/47.5	98.8	N/A	N/A	N/A	56.6	91.6	32.0	7.1	8.0	64	9.5	Yes	N/A	N/A	N/A	N/A
Harris et al.[35]	IDegLira 1WT (n=210)	53/47	N/A	N/A	N/A	N/A	56.6	95.9	32.4	7.4	8.2	65.6	10.1	94.3	5.7	N/A	N/A	N/A
	IDegLira 2WT (n=210)	53/47	N/A	N/A	N/A	N/A	57.0	95.2	32.5	7.2	8.1	64.5	10.1	95.2	4.8	N/A	N/A	N/A
Rodbard et al.[31]	IDegLira (n=289)	53.3/46.7	75.5%	5.5%	18.0%	1.4%	60.0	87.2	31.2	9.0	7.9	63	9.1	N/A	N/A	N/A	10.4	(a)
	Placebo (n=146)	50.0/50.0	76.0%	8.9%	13.7%	1.4%	59.4	89.3	32.0	9.3	7.9	63	9.1	N/A	N/A	N/A	11.6	(a)
Billings et al.[34]	IDegLira (n=252)	43.7/56.3	N/A	N/A	N/A	N/A	58.6	87.2	31.7	13.2	8.2	66	8.5	Yes	N/A	N/A	N/A	N/A
	IGlar U100 + IAsp (n=254)	46.1/53.9	N/A	N/A	N/A	N/A	58.0	88.2	31.7	13.3	8.2	67	8.3	Yes	N/A	N/A	N/A	N/A
Aroda et al.[33]	IDegLira (n=506)	55/45	N/A	N/A	N/A	N/A	56.8	89.7	32.0	10.0	8.4	68.1	9.9	98%	8%	N/A	63%	(b), (d), (e)
	IGlar U100 (n=506)	54/46	N/A	N/A	N/A	N/A	56.4	89.0	31.9	10.2	8.6	70.5	10.2	98%	8%	N/A	66%	(b), (d), (e)
Philis-Tsimikas et al.[32]	IDegLira (n=210)	57.6/42.4	83.3	1.4	14.8	0.5	56.1	89.3	31.5	9.8	8.2	66.1	9.5	Yes	N/A	N/A	N/A	(f), (g), (h), (i)
	Iglar U100 (n=210)	60/40	81.4	1.0	16.7	1.0	57.2	87.2	30.9	9.3	8.4	67.9	9.6	Yes	N/A	N/A	N/A	(f), (g), (h), (i)
Kaku et al.[23]	IDegLira (n=275)	70.5/29.5	N/A	N/A	N/A	N/A	56.9	70.7	26.1	9.2	8.5	69.6	9.9	17.1%	N/A	N/A	15.6%	(b), (c), (e), (j)
	Degludec (n=271)	72.0/28.0	N/A	N/A	N/A	N/A	57.8	72.6	26.6	9.7	8.5	69.7	10.0	17.0%	N/A	N/A	15.5%	(b), (c), (e), (j)
	Liraglutide (n=273)	70.3/29.7	N/A	N/A	N/A	N/A	56.8	72.2	26.5	9.4	8.3	67.4	9.7	17.2%	N/A	N/A	15.4%	(b), (c), (e), (j)
Watada et al.[30]	IDegLira (n=105)	66.7/33.3	N/A	N/A	N/A	N/A	56.6	73.9	27.3	14.33	8.61	70.57	8.95	N/A	N/A	N/A	N/A	(k), (l), (m), (n)

	Degludec (n=105)	60.0/40.0	N/A	N/A	N/A	N/A	55.5	75.5	28.1	13.77	8.56	70.06	8.64	N/A	N/A	N/A	N/A	(k), (l), (m), (n)
	Total (n=210)	63.3/36.7	N/A	N/A	N/A	N/A	56.0	74.7	27.7	14.05	8.58	70.32	8.79	N/A	N/A	N/A	N/A	(k), (l), (m), (n)
NCT02911948	IDegLira (n=105)	66.7/33.3	0	0	105	0	56.6	N/A	N/A	N/A	8.61	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Insulin Degludec (n=105)	60.0/40.0	0	0	105	0	55.5	N/A	N/A	N/A	8.56	N/A	N/A	N/A	N/A	N/A	N/A	N/A
NCT02787551	IGlarLixi (n=257)	49.0/51.0	241	12	3	2	59.2	N/A	27.6%	11.23	7.78	N/A	N/A	Yes	N/A	N/A	N/A	N/A
	GLP-1 RA (n=257)	56.0/44.0	244	7	4	2	60.0	N/A	26.8%	10.95	7.80	N/A	N/A	Yes	N/A	N/A	N/A	N/A

Footnotes: (a) Sulphonylurea plus metformin, (b) Glinide, (c) SGLT-2 Inhibitor, (d) DPP-4 Inhibitor, (e) α-glucosidase inhibitor, (f) SGLT2 Inhibitor ± Pioglitazone, (g) SGLT2 inihibitor + metformin ± pioglitazone, (h) SGLT2 inhibitor + DPP-4 ± pioglitazone, (i) SGLT2 Inhibitor + metformin + DPP-4 inhibitor ± pioglitazone, (j) Thiazolidinediones, (k) Metformin and Basal Insulin, (l) Metformin + basal insulin + 1 other OAD,
(m) Metformin + pre=mix/combination insulin (n) Metfor min + pre-mix/combination insulin + 1 other OAD