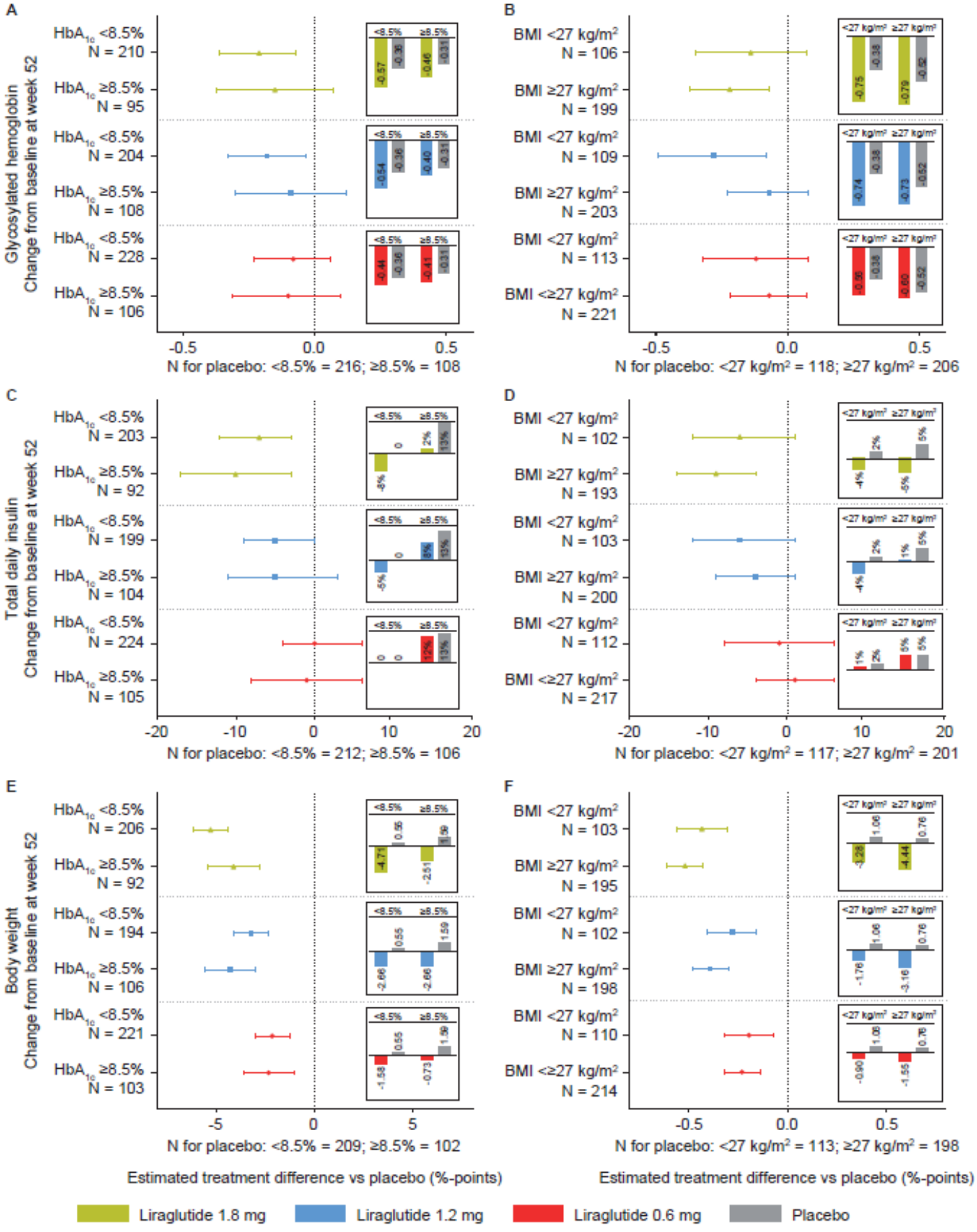
Efficacy and Safety of Liraglutide in Type 1 Diabetes by Baseline Anthropometrics in the ADJUNCT ONE and ADJUNCT TWO Randomized Controlled Trials

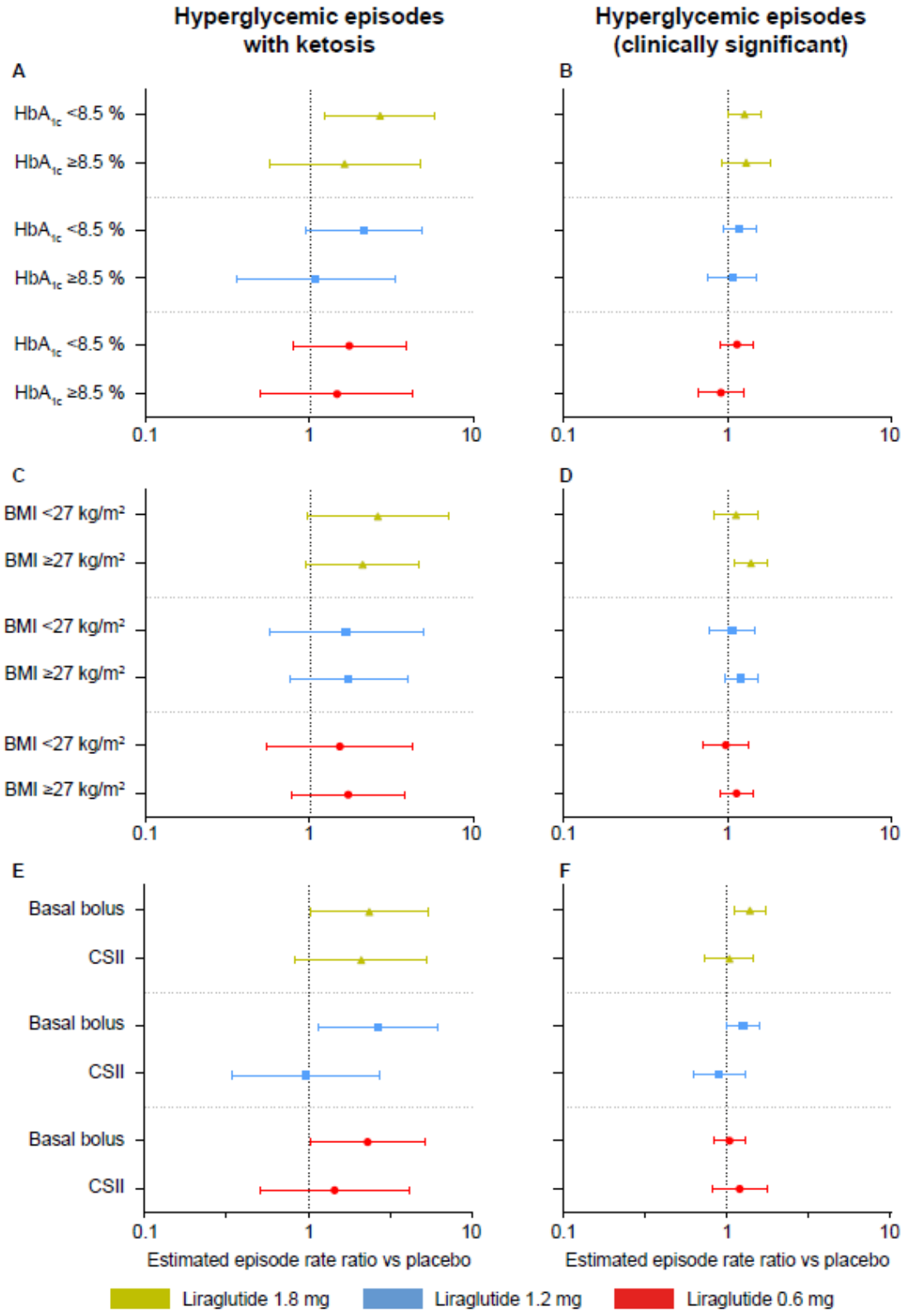
Supplemental Material

Figure S1. Glycosylated hemoglobin, insulin use and body weight in ADJUNCT ONE – week 52



Data are estimated mean changes from baseline (bars) and estimated treatment differences versus placebo with 95% confidence intervals (forest plot) at week 52 in ADJUNCT ONE. Estimates are shown for change in HbA_{1c} (panels A and B), total daily insulin dose (panels C and D) and body weight (panels E and F) by subgroups by baseline HbA_{1c} level (HbA_{1c} < or ≥8.5% [69 mmol/mol]) and by baseline BMI (BMI < or ≥27 kg/m^2). Estimates were derived from a mixed model for repeated measurements with treatment, subgroup, stratification, visit and country as fixed factors and baseline value as a fixed covariate; the model also included the interaction between subgroup and treatment group, and the interactions between each model term and visit, and group mean estimates were adjusted according to the observed baseline distribution in each subgroup. Post-baseline on-treatment data (data collected on or after the first day on treatment and no later than the day after the last day on treatment) were included in the analysis. The estimated placebo-adjusted treatment effect did not differ statistically significantly within subgroups for all liraglutide dose levels (all tests for interaction between treatment and group were not statistically significant).
BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; *N*, number of participants.

Figure S2. Hyperglycemia with ketosis and hypoglycemia (clinically significant) in ADJUNCT ONE – week 52



Data are estimated mean rate ratios versus placebo with 95% confidence intervals at week 52 in ADJUNCT ONE. Estimates are shown for hyperglycemic episodes with ketosis (episodes with plasma glucose >16.7 mmol/L and plasma ketone >1.5 mmol/L; panels A, C and E) and clinically significant hypoglycemic episodes (panels B, D and F;

symptomatic hypoglycemic episodes as defined by Novo Nordisk as severe according to ADA and a plasma glucose value <3.1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycemia [ref 1]) by subgroups by baseline HbA_{1c} level (HbA_{1c} < or ≥8.5% [69 mmol/mol]), by baseline BMI (BMI < or ≥27 kg/m^2) and by type of insulin treatment used at baseline (basal bolus or CSII). Episodes are treatment-emergent (onset on or after the first day on treatment and no later than the day after the last day on treatment). Estimates were derived from a negative binomial regression model with a log-link and with treatment, subgroup, country, stratification factor, and the interaction between treatment and subgroup as factors, baseline HbA_{1c} as a covariate, and the logarithm of the exposure time as offset. The episode rate ratios did not differ statistically significantly within subgroups for all liraglutide dose levels (*p*-value for test for interaction between subgroup and treatment group >0.05). ADA, American Diabetes Association; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA_{1c}, glycosylated hemoglobin.

Table S1. Glycosylated hemoglobin, body weight and total daily insulin dose – ADJUNCT ONE – week 26 – all participants

	Liraglutide			Placebo
	1.8 mg	1.2 mg	0.6 mg	
HbA_{1c} (%)				
Baseline	8.1	8.2	8.2	8.2
Mean at week 26	7.4	7.4	7.6	7.7
Change from baseline	-0.78	-0.72	-0.59	-0.48
Treatment difference vs placebo	-0.30 [-0.41; -0.19] $p < 0.0001$	-0.24 [-0.36; -0.13] $p < 0.0001$	-0.11 [-0.22; -0.01] $p = 0.0380$	-
HbA_{1c} (mmol/mol)				
Baseline	65	66	66	66
Mean at week 26	57	57	60	61
Change from baseline	-8.5	-7.9	-6.4	-5.2
Treatment difference vs placebo	-3.32 [-4.5; -2.1] $p < 0.0001$	-2.68 [-3.9; -1.5] $p < 0.0001$	-1.24 [-2.4; -0.1] $p = 0.0380$	-
Body weight (kg)				
Baseline	86.3	85.4	86.5	86.4
Mean at week 26	81.5	82.9	84.3	86.5
Change from baseline	-4.7	-3.3	-2.0	0.3
Treatment difference vs placebo	-5.0 [-5.6; -4.5] $p < 0.0001$	-3.6 [-4.2; -3.0] $p < 0.0001$	-2.2 [-2.8; -1.7] $p < 0.0001$	-
Total daily insulin dose (U)				
Baseline	58.2	56.9	58.2	58.5
Mean at week 26	51.9	54.4	56.9	59.2
Change from baseline	-10%	-6%	-2%	2%
Treatment difference vs placebo	-12% [-16%; -9%] $p < 0.0001$	-8% [-12%; -4%] $p < 0.0001$	-4% [-8%; 0%] $p = 0.0470$	-

Table S2. Hyperglycemia with ketosis and clinically significant hypoglycemia – ADJUNCT ONE – week 26 – all participants

	Liraglutide			Placebo
	1.8 mg	**1.2 mg**	**0.6 mg**	
Hyperglycemia with ketosis				
Number of participants with episodes	28	19	17	20
Number of episodes	51	27	43	31
Episode rate ratio vs placebo	1.84 [0.86; 3.92] $p = 0.1156$	1.15 [0.51; 2.60] $p = 0.7287$	1.51 [0.72; 3.20] $p = 0.2776$	-
Hypoglycemia (clinically significant)				
Number of participants with episodes	299 (86%)	291 (84%)	281 (80%)	282 (81%)
Number of episodes	3852	3591	3552	3213
Episode rate ratio vs placebo	1.34 [1.10; 1.63] $p = 0.0033$	1.29 [1.06; 1.57] $p = 0.0125$	1.18 [0.97; 1.43] $p = 0.0995$	-

Reference:

1. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R: Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384-1395