SUPPLEMENTARY DATA

Redefining hypoglycemia in clinical trials: validation of definitions recently adopted by American Diabetes Association/European Association for the Study of Diabetes

Supplementary appendix:

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Supplementary Table S1: SWITCH and DEVOTE trial summary

	SWITCH 1 and 2	DEVOTE
Trial design	Double-blind, randomized, two-period crossover, multicenter, treat-to-target clinical trials	Double-blind, randomized, active comparator, treat-to-target cardiovascular outcomes trial
Trial duration	Time dependent: 64-weeks • Two treatment periods (32 weeks each) each consisting of a 16-week titration period (Weeks 1–16 and Weeks 33–48) and a 16-week maintenance period (Weeks 17–32 and Weeks 49–64)	Event driven: Continue until at least 633 MACE had accrued
Comparators	Degludec versus glargine U100	Degludec versus glargine U100
Inclusion criteria	**SWITCH 1:** • Type 1 diabetes • HbA_{1c} levels of ≤10% • BMI ≤45 kg/m^2 • Basal–bolus regimen or continuous subcutaneous insulin infusion for ≥26 weeks **SWITCH 2:** • Insulin-experienced patients with type 2 diabetes • HbA_{1c} levels of ≤9.5% • BMI ≤45 kg/m^2 • Any basal insulin with or without OADs (any combination of metformin, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, thiazolidinediones, and sodium glucose cotransporter-2 inhibitor) **SWITCH 1 and 2:** At least 1 of the following risk factors for hypoglycemia: • ≥1 severe hypoglycemic events	• Type 2 diabetes • Treated with ≥1 oral or injectable antihyperglycemic agent • HbA_{1c} ≥7.0%, or with ≥20 units/day of basal insulin • ≥1 co-existing cardiovascular or renal condition and were aged ≥50 years • OR ≥1 of a list of pre-specified cardiovascular risk factors and were aged ≥60 years • Patients were not excluded if they had experienced severe hypoglycemia prior to randomization

	within the last year • Moderate chronic renal failure • Hypoglycemia symptom unawareness • Diabetes duration >15 years (SWITCH 1)/Insulin use >5 years (SWITCH 2) • Hypoglycemic event within the last 12 weeks	
References	(1,2)	(3,4)

BMI, body mass index; MACE, major adverse cardiovascular event; OAD, oral antidiabetes drug.

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Supplementary Table S2: Hypoglycemia definitions applied to the SWITCH and DEVOTE trial data

Hypoglycemia definitions applied in this secondary analysis		SWITCH	DEVOTE	References
ADA 2005	Events confirmed by a PG of ≤3.9 mmol/L with symptoms	✓		5
Level 2	Events confirmed by a glucose of <3.0 mmol/L	✓		6
Level 3	Events requiring third-party assistance (ADA)	✓[a,b]	✓[a,b]	6,7
Novo Nordisk	Events confirmed by a PG of <3.1 mmol/L with symptoms or events that are severe, requiring third-party assistance (ADA)	✓[b]		1,2

ADA, American Diabetes Association; PG, plasma glucose.
[a]Adjudicated by a central, blinded, independent Event Adjudication Committee.
[b]Pre-specified definition.

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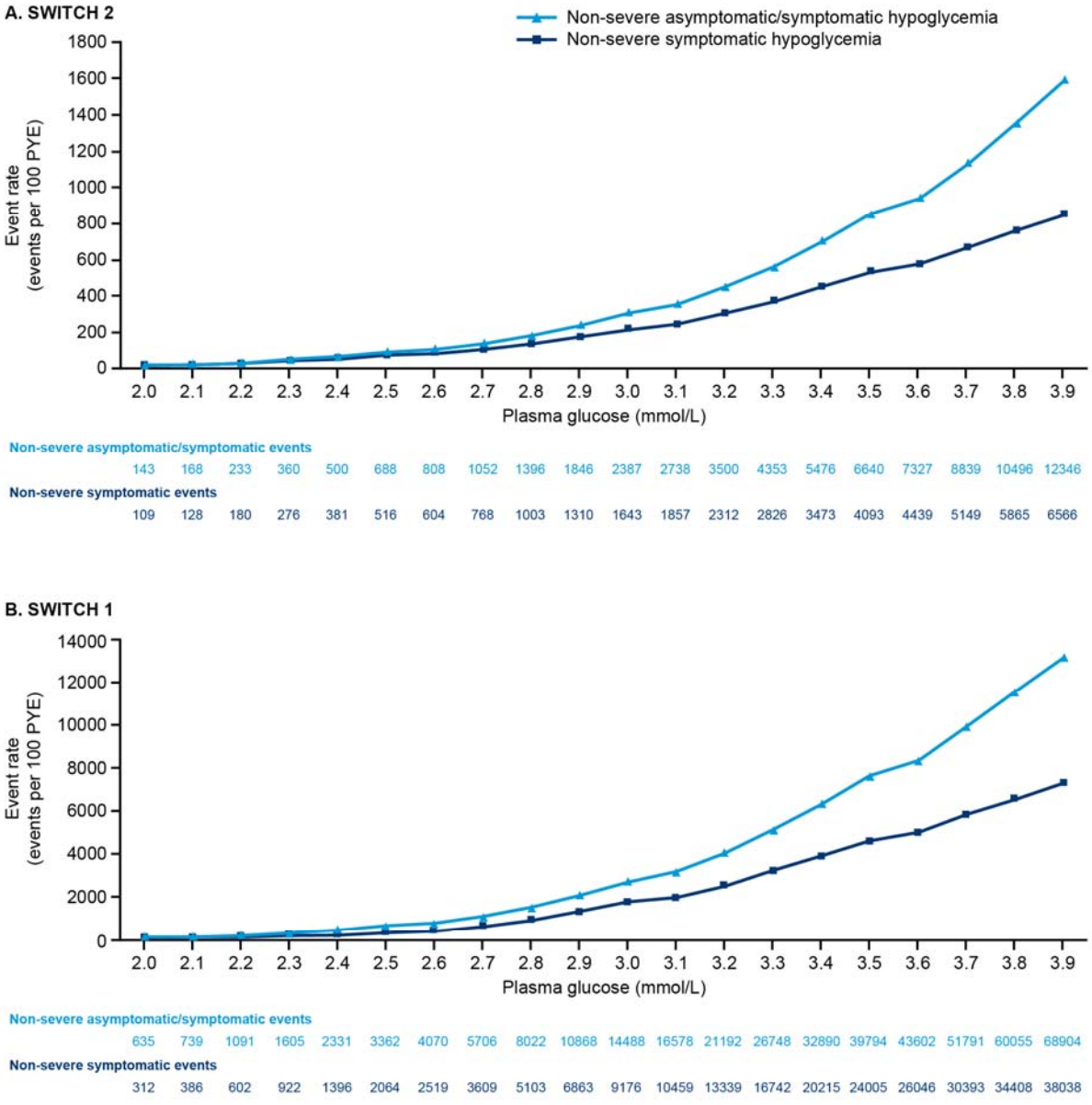
Supplementary Figure S1: Non-severe hypoglycemic events (total and symptomatic) in the total treatment period of SWITCH 2 and 1 at different plasma glucose levels in a pooled randomized treatment dataset



The event rates in the pooled randomized treatment dataset (degludec and glargine U100) are plotted at a given plasma glucose level or lower.
PYE, patient year of exposure.

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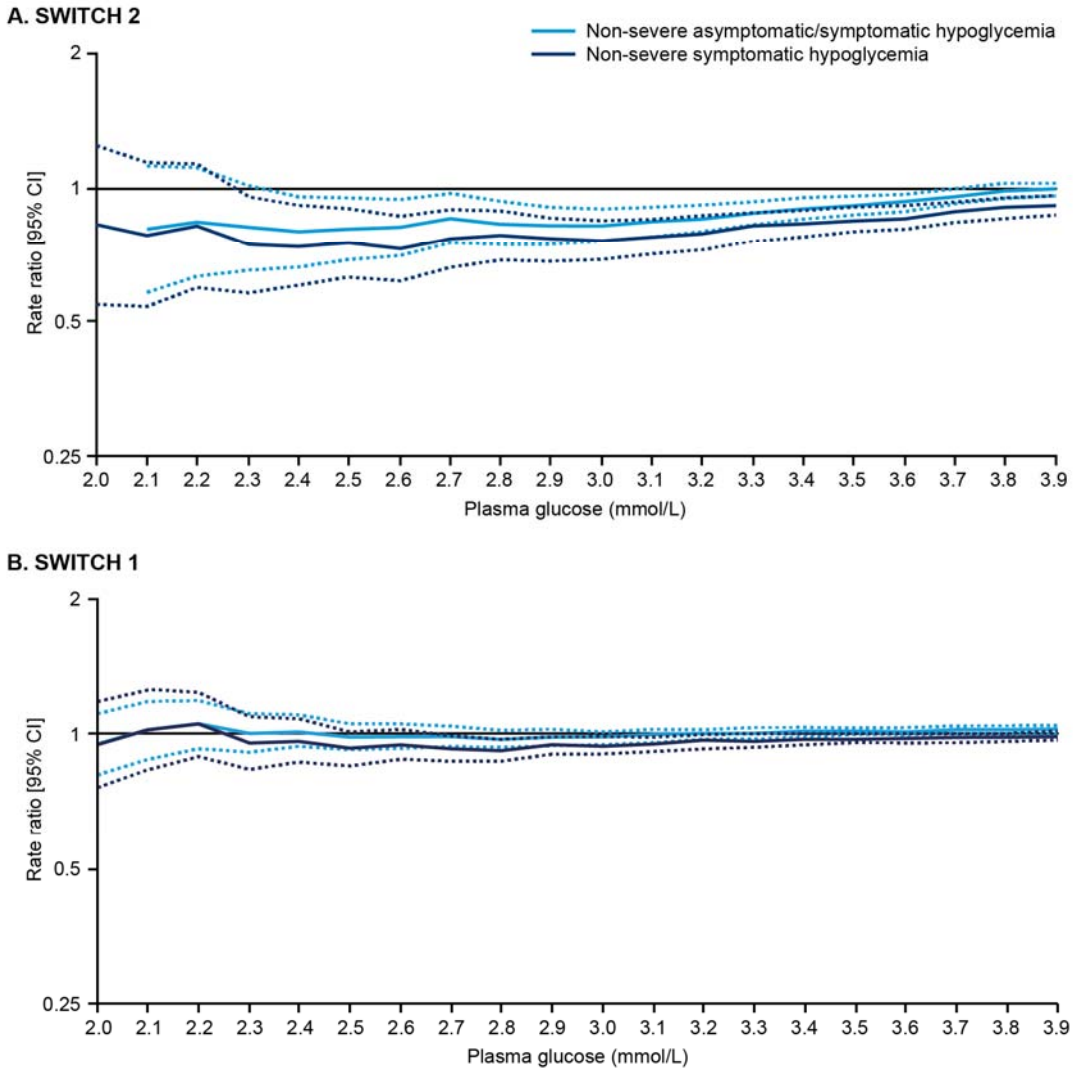
Supplementary Figure S2: Estimated rate ratios of non-severe hypoglycemic events (total and symptomatic; degludec versus glargine U100) in the total treatment period of SWITCH 2 and 1 at different plasma glucose levels



The solid lines represent the estimated rate ratio (degludec versus glargine U100) at different plasma glucose levels. The dashed lines represent the upper and lower 95% confidence intervals.
Glargine U100, insulin glargine 100 units/mL.

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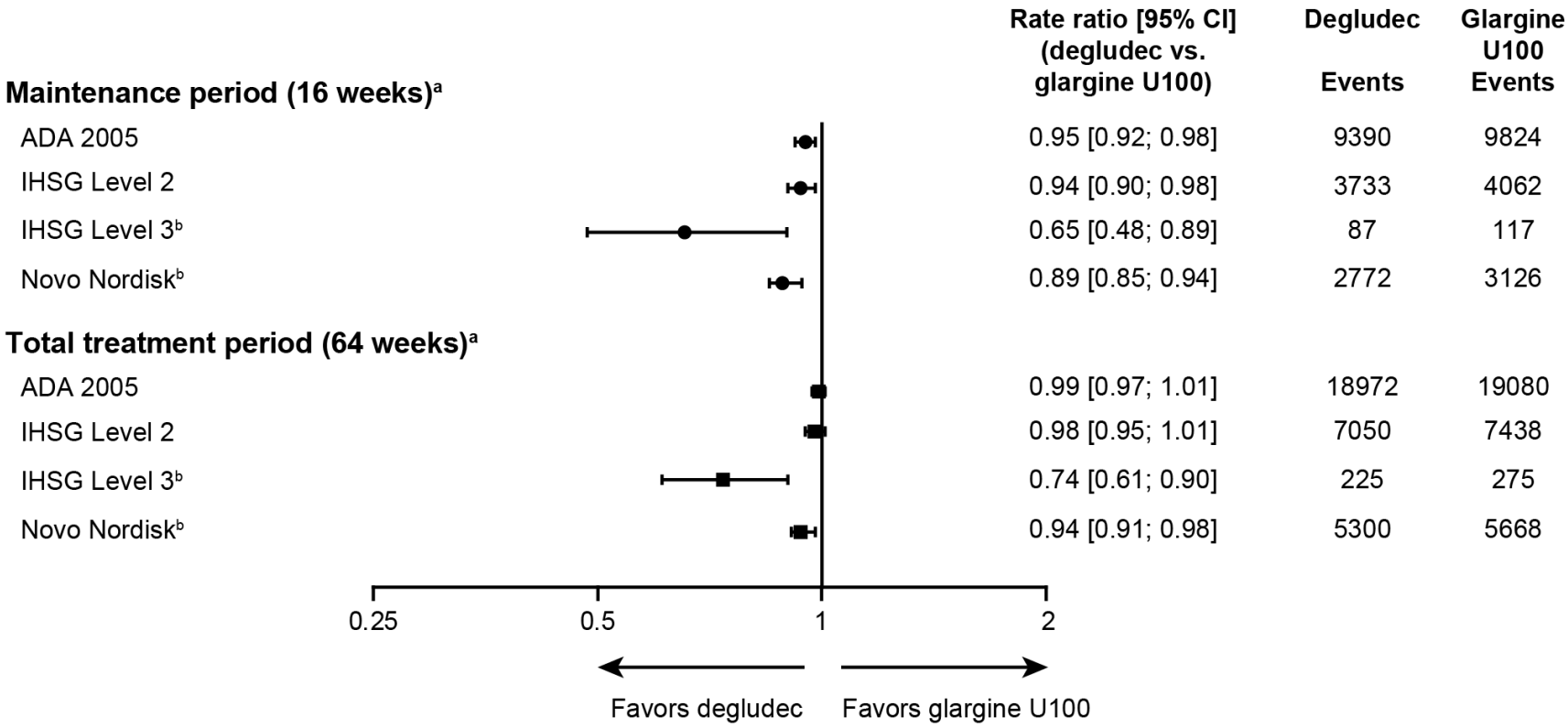
Supplementary Figure S3: Hypoglycemic events in SWITCH 1 by treatment group



[a]The total trial duration was 64 weeks; this included 32 weeks' treatment with once-daily degludec or glargine U100 followed by crossover to glargine U100 or degludec, respectively, for a further 32 weeks. Each 32-week treatment period consisted of a 16-week titration period and a 16-week maintenance period.

[b]Pre-specified hypoglycemia definition as used during the original trial.

ADA 2005: plasma glucose ≤3.9 mmol/L with symptoms; IHSG Level 2: glucose <3.0 mmol/L; IHSG Level 3: severe events requiring third-party assistance intervention independent of a defined glucose; Novo Nordisk: plasma glucose <3.1 mmol/L with symptoms plus severe events.

Glargine U100, insulin glargine 100 units/mL.

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References

1. Lane W, Bailey TS, Gerety G, *et al*. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. JAMA 2017;318:33–44.
2. Wysham C, Bhargava A, Chaykin L, *et al*. Effect of Insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA 2017;318:45–56.
3. Marso SP, McGuire DK, Zinman B, *et al*. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) – DEVOTE 1. Am Heart J 2016;179:175–183
4. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017;377:723–732.
5. American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–1249.
6. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–157.
7. Seaquist ER, Anderson J, Childs B, *et al*. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–1395.