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Supplementary Table 1. Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:

1. Are currently taking oral antidiabetes medication that is not described in inclusion criteria and not allowed with concurrent use of insulin per local product label.

2. Have taken more than 1 week within 1 month prior to visit 1 any glucose-lowering medications not included in inclusion criteria (for example, those not approved for use with insulin, rosiglitazone, rimonabant, acarbose, miglitol, pramlintide, repaglinide, nateglinide or dipeptidyl peptidase-4 inhibitors, or pioglitazone) either alone or in combination formulations, or have used a drug for weight loss (for example, prescription drugs such as orlistat, sibutramine, phenylpropanolamine, rimonabant, or similar over-the-counter medications).

3. Have taken any insulin other than glargine within the 3 months prior to visit 1 for more than 1 week.

4. Are receiving chronic (lasting longer than 2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, and inhaled preparations) within 4 weeks prior to visit 1.

5. Have had a clinically significant history of cardiac disease with functional status that is Class III or IV (New York Heart Association Class III or IV) (see Protocol Attachment 5) or considered by the investigator to be exclusionary.

6. Have had more than 1 episode of major hypoglycaemia, as defined in the Abbreviations and Definitions section, within 6 months prior to visit 1.

7. Female patients with a positive pregnancy test and/or intending to become pregnant or sexually active and not using birth control throughout the study to prevent pregnancy.

8. Women who are breastfeeding.

9. Have any of the following concomitant diseases: presence of clinically significant hematologic, oncologic, renal (or have creatinine clearance below 30 ml/min), cardiac, hepatic or gastrointestinal disease or any other serious disease considered by the investigator to be exclusionary.

10. Have fasting triglyceride levels >500 mg/dL (>5.64 mmol/L).

11. Have a history of renal transplantation or are currently receiving renal dialysis.

12. Have a history of confirmed pancreatitis.

13. Have an active or untreated malignancy, or have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years.

14. Have contraindication or known hypersensitivity or allergy to exenatide or to any of the product components (including prior withdrawal of exenatide therapy after experiencing adverse events).

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15. Have had a blood transfusion or severe blood loss within 3 months prior to visit 1 or have known hemoglobinopathy, hemolytic anemia, or sickle cell anemia, or any other condition known to interfere with the glycated hemoglobin methodology.

16. Have any other condition (including known drug or alcohol abuse or psychiatric disorder) that precludes the patient from following and completing the protocol, according to the investigator's judgment.

17. Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an off-label use of an investigational drug or device (other than the study drug/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

18. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

19. Are employed by Eli Lilly and Company or Amylin Pharmaceuticals, Inc. (Amylin) (that is, employees, temporary contract workers, or designees responsible for conducting the study).

20. Have previously completed or been withdrawn from this study after enrollment.

21. If on metformin and have contraindication to metformin use, including known metabolic or lactic acidosis, or any condition associated with hypoperfusion, hypoxemia, dehydration, or sepsis.

22. Have had a radiologic contrast study performed within 48 hours prior to visit 1.

23. Have any exclusion required by local law.

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Supplementary Table 2. Definitions of hypoglycemia

Major hypoglycemia: Any episode with symptoms consistent with hypoglycemia resulting in loss of consciousness or seizure that showed prompt recovery in response to administration of glucagon or glucose or documented hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL]) as measured with Roche plasma-equivalent test strips (corresponding to 3.2 mmol/L [53 mg/dL] in Roche "IFCC" plasma-equivalent values or 2.9 mmol/L [53 mg/dL] in whole blood) and requiring the assistance of another person because of severe impairment in consciousness or behavior (whether or not symptoms of hypoglycemia were detected by the patient).
Minor hypoglycemia: Any time a patient feels that he or she is experiencing a sign or symptom associated with hypoglycaemia that is either self-treated by the patient or resolves on its own and has a concurrent finger stick blood glucose <3.0 mmol/L (54 mg/dL) as measured with Roche plasma-equivalent test strips. This corresponds to 3.2 mmol/L (59 mg/dL) in Roche "IFCC" plasma-equivalent values or 2.9 mmol/L (53 mg/dL) in whole blood.
Symptoms of hypoglycemia: Any reported hypoglycemic episode that did not fit into the above definitions of major or minor hypoglycemia. Note: Hypoglycemic episodes with related blood glucose value as missing were classified as symptoms of hypoglycemia.
Nocturnal hypoglycemia: Any hypoglycemic event that occurred between bedtime and waking. Signs and symptoms of hypoglycemia not confirmed with blood glucose values are reported separately from the confirmed episodes described above.
Non-nocturnal (daytime) hypoglycemia: Any hypoglycemic event that occurred between waking and bedtime. Signs and symptoms of hypoglycemia not confirmed with blood glucose values are reported separately from confirmed episodes described above.

IFCC = International Federation of Clinical Chemistry and Laboratory Medicine.

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Supplementary Table 3. Efficacy measures for the intention-to-treat population at randomization and at 30 weeks

Characteristic or Variable	At Randomization		At End of Study (30 wk)		
	Exenatide (n=315)	Lispro (n=312)	Exenatide (n=315)	Lispro (n=312)	Exenatide–Lispro
HbA1c (%) [mmol/mol]	8.3 (1.0) [67 (11)]	8.2 (0.9) [66 (10)]	7.1 (0.9) [54 (10)]	7.1 (0.8) [54 (9)]	--
Change from randomization HbA1c (%) [mmol/mol]	--	--	–1.10 (0.05) [-12.0(0.5)]	–1.07 (0.05) [-11.7(0.5)]	–0.03 (–0.16, 0.11)
FG (mmol/L)	7.2 (2.4)	7.0 (2.5)	6.5 (2.3)	7.2 (2.8)	--
Change from randomization FG (mmol/L)	--	--	–0.39 (0.16)	0.26 (0.15)	–0.65 (–1.06, –0.24)
Body weight (kg)	89.9 (16.7)	89.3 (17.3)	89.0 (1.1)	93.0 (1.1)	--
Change from randomization body weight (kg)	--	--	–2.6 (0.2)	1.9 (0.2)	–4.5 (–5.2, –3.9)

Values are mean (SD) at randomization or end of study, and Least Squares (LS) mean (SE) for exenatide and lispro or LS mean (95% CI) for exenatide–lispro for change from randomization at end of study.
FG = fasting glucose; HbA1c = glycated hemoglobin A1c.

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Supplementary Table 4. Summary of Treatment Emergent Adverse Events

	Exenatide (n=315)	Lispro (n=312)
Patients with at least one TEAE, n (%)	228 (72.4)	175 (56.1)*
Patients with at least one TEAE possibly related to study drug, n (%)	131 (41.6)	13 (4.2)*
Patients with at least one serious TEAE, n (%)	18 (5.7)	23 (7.4)
Discontinuation due to TEAEs,† n (%)	17 (5.4)	8 (2.6)
Acute myocardial infarction	0 (0.0)	1 (0.3)
Nausea	9 (2.9)	0 (0.0)
Vomiting	2 (0.6)	0 (0.0)
Diarrhea	1 (0.3)	0 (0.0)
Dry mouth	0 (0.0)	1 (0.3)
Cholecystitis chronic	0 (0.0)	1 (0.3)
Urinary tract infection	0 (0.0)	1 (0.3)
Lower limb fracture	1 (0.3)	0 (0.0)
Decreased appetite	1 (0.3)	0 (0.0)
Gout	0 (0.0)	1 (0.3)
Pancreatic carcinoma	1 (0.3)	0 (0.0)
Dizziness	1 (0.3)	0 (0.0)
Fear of weight gain	0 (0.0)	1 (0.3)
Dermatitis allergic	1 (0.3)	0 (0.0)
Rash generalized	0 (0.0)	1 (0.3)
Coronary artery bypass	0 (0.0)	1 (0.3)
Frequent TEAEs (≥5%), n (%)		
Nausea	102 (32.4)	5 (1.6)
Vomiting	39 (12.4)	3 (1.0)
Diarrhea	34 (10.8)	16 (5.1)
Dyspepsia	19 (6.0)	3 (1.0)
Nasopharyngitis	37 (11.7)	20 (6.4)
Bronchitis	18 (5.7)	6 (1.9)
Influenza	18 (5.7)	16 (5.1)
Headache	18 (5.7)	11 (3.5)
Serious TEAEs in 2 or more patients, n (%)		
Acute myocardial infarction	0 (0.0)	2 (0.6)
Urinary tract infection	1 (0.3)	1 (0.3)
Pneumonia	0 (0.0)	2 (0.6)
Nephrolithiasis	0 (0.0)	2 (0.6)
Hypoglycemia (number of events)		
Major	3	11
Minor	332	870‡
Nocturnal confirmed	232	297
Non-nocturnal confirmed	103	584§

A treatment-emergent adverse event (TEAE) was defined as an adverse event that first occurred or worsened after randomization. *p<0.001 lispro versus exenatide. †One patient with pancreatic carcinoma. ‡p=0.004 exenatide versus lispro. §p<0.001 exenatide versus lispro.

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Supplementary Table 5. Patient-reported outcomes for treatment satisfaction and weight-related quality of life

Parameter	Exenatide	Lispro	Exenatide - Lispro
Mean (SD) baseline DTSQ total score	26·7 (6.96)	27·3 (6.43)	
LS mean (SE) change in DTSQ total score	2.19 (0.18)*	1.40 (0.18)*	0.80 (0.23)†
LS mean (SE) change from baseline in:			
1. Treatment satisfaction--current	0.48 (0.04)*	0.33 (0.04)*	0.15 (0.05)†
2. Perceived frequency high blood sugar	–0.78 (0.06)*	–0.59 (0.06)*	–0.19 (0.07)†
3. Perceived frequency low blood sugar	0.06 (0.05)	0.19 (0.05)*	–0.13 (0.07)‡
4. Treatment convenience	0.29 (0.04)*	0.13 (0.04)*	0.16 (0.05)†
5. Treatment flexibility	0.27 (0.04)*	0.13 (0.·04)	0.14 (0.05)†
6. Understanding of diabetes	0.38 (0.04)*	0.29 (0.04)*	0.09 (0.05)‡
7. Treatment recommend	0.38 (0.04)*	0.27 (0.04)*	0.11 (0.05)‡
8. Treatment satisfaction--continue	0.37 (0.04)*	0.23 (0.04)*	0.14 (0.05)†
Mean (SD) baseline IWQOL total score	80.00 (18.74)	80.00 (19.72)	
LS mean (SE) change in IWQOL total score	4.40 (0.80)*	0.51 (0.80)	3.88 (1.02)†
LS mean (SE) change from baseline in:			
Physical function	5.48 (0.96)*	1.66 (0.95)	4.84 (1.41)†
Self-esteem	4.76 (0.93)*	1.51 (0.92)	5.17 (1.37)†
Sexual life	2.83 (1.25)*	1.10 (1.25)	1.40 (1.94)
Public distress	0.93 (0.71)	0.16 (0.71)	1.69 (1.07)
Work	2.72 (0.82)*	0.15 (0.81)	3.28 (1.27)†

SD = standard deviation, LS = least squares, SE = standard error

DTSQ total score 0–36 with higher scores indicating higher treatment satisfaction (positive change indicates improvement). All DTSQ items scored 0–6 with higher scores better (positive change indicates improvement), except "perceived frequency high blood sugar" and "perceived frequency low blood sugar" where lower scores better (negative Δ indicates improvement). These two items do not contribute to total DTSQ score.

IWQOL total score and domain scores 0–100 with higher scores indicating lower perceived impact of weight on quality of life. Positive change indicates improvement.

Change ITT from MMRM (treatment group × visit interaction) for change from baseline to week 30 (DTSQ baseline = start of BIO-phase; IWQOL baseline = randomization). *$p<0.05$ for baseline to Week 30, defined by 95% confidence interval not spanning 0. †$p<0.01$ for exenatide versus lispro. ‡$p<0.05$ for exenatide versus lispro

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Supplementary Table 6. HbA1c (%) by anti-exenatide antibody status

	Anti-exenatide antibody status (N=315)			
Visit	Positive (All) (n=70)	Positive (Low titer) (n=60)	Positive (High titer) (n=10)	Negative (n=234)
Randomization				
n	70	60	10	234
Mean (SD)	8.6 (1.16)	8.7 (1.16)	8.5 (1.21)	8.2 (0.89)
Endpoint (ITT)				
n	62	54	8	203
Mean (SD)	7.5 (0.88)	7.5 (0.83)	7.9 (1.15)	7.0 (0.85)
Endpoint (ITT LOCF)				
n	70	60	10	234
Mean (SD)	7.5 (0.87)	7.4 (0.79)	7.9 (1.20)	7.2 (0.97)
Change from randomization to endpoint				
n	62	54	8	203
Mean (SD)	–1.2 (1.00)	–1.2 (1.00)	–0.7 (0.86)	–1.1 (0.87)
Change from randomization to endpoint (LOCF)				
n	70	60	10	234
Mean (SD)	–1.1 (0.97)	–1.2 (0.96)	–0.6 (0.82)	–1.0 (0.85)

HbA1c = glycated hemoglobin A1c; ITT=intention-to-treat; LOCF=last observation carried forward.

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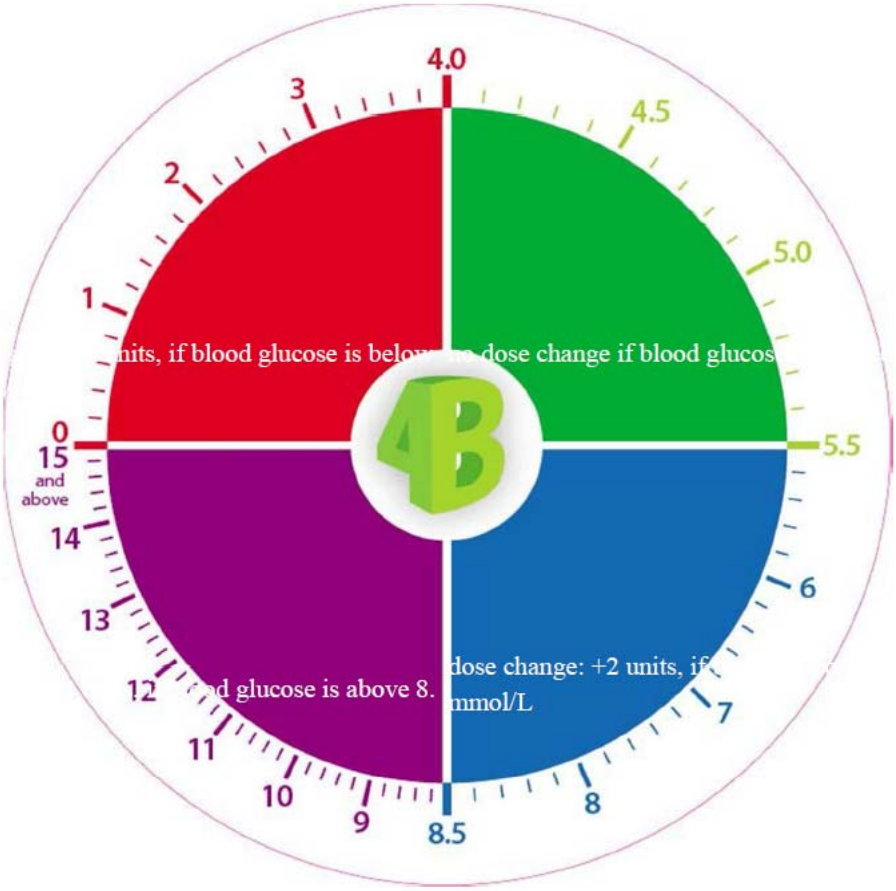
Supplementary Figure 1. Titration algorithm for basal insulin glargine

The following instructions were given to the participants with respect to the use of the wheel to help them to decide with the study doctor or nurse to adjust their dose of insulin glargine.

- Please take your insulin glargine at bedtime, as instructed by your study doctor or nurse.
- Record daily: date of dose, time of dose, and treatment dose in number of units in your diary.
- Please use the wheel for insulin glargine for blood glucose levels (measured before breakfast) or fasting glucose.
- Please test your fasting blood glucose every morning before you eat or drink anything. Fasting means that you have not had anything to eat or drink for at least 8 hours, except water.
- The dose change (if any) is based on the average value of three consecutive fasting blood glucose levels.
- If fasting blood glucose is lower than 4.0 mmol/L [72 mg/dL] and you have signs or symptoms of low blood glucose that occurs without reason, decrease dose of insulin glargine by 2 units.



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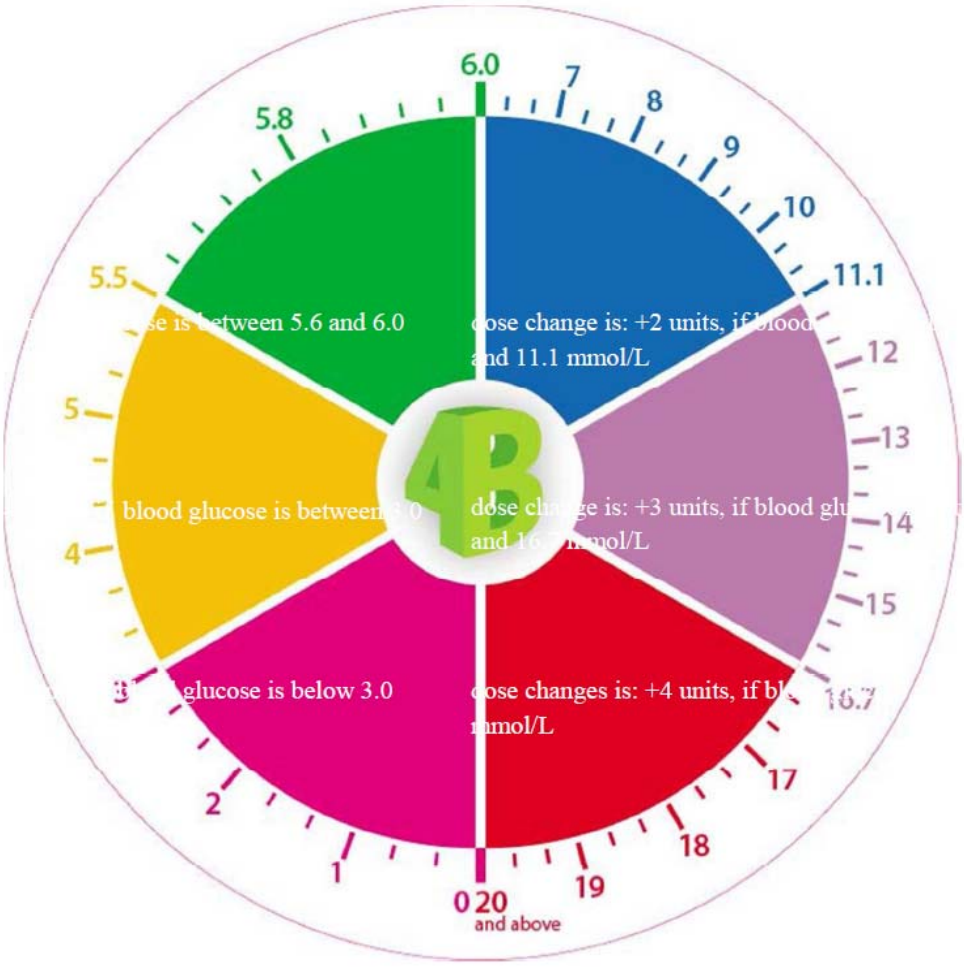
Supplementary Figure 2. Titration algorithm for thrice-daily insulin lispro

The following instructions were given to the participants with respect to the use of the wheel to help them to decide with the study doctor or nurse to adjust their dose of insulin lispro.

- Please take insulin lispro before breakfast, before lunch, and before dinner as instructed by your study doctor and nurse.
- Record daily: date of dose, time of dose, and treatment dose in number of units in your diary.
- Please test your blood glucose levels four times a day twice a week: fasting before breakfast, before lunch, before dinner, and at bedtime. Test your blood glucose immediately before injections and before you start a meal.
- For example, if before lunch the blood glucose is in the range of 109–200 mg/dL, the next day the insulin dose of lispro before breakfast should be increased by 2 units. If before dinner the blood glucose is in the range of 109–
200 mg/dL, the next day the insulin dose of lispro before lunch should be increased by 2 units. If before bedtime the blood glucose is in the range of 6.1–11.1 mmol/L [109–200 mg/dL], the next day the insulin dose of lispro before
dinner should be increased by 2 units.
- Please use the wheel for insulin lispro for blood glucose levels, measured before lunch, before dinner, and at bedtime.
- Please use the wheel for insulin glargine for blood glucose levels (measured before breakfast) or fasting glucose.



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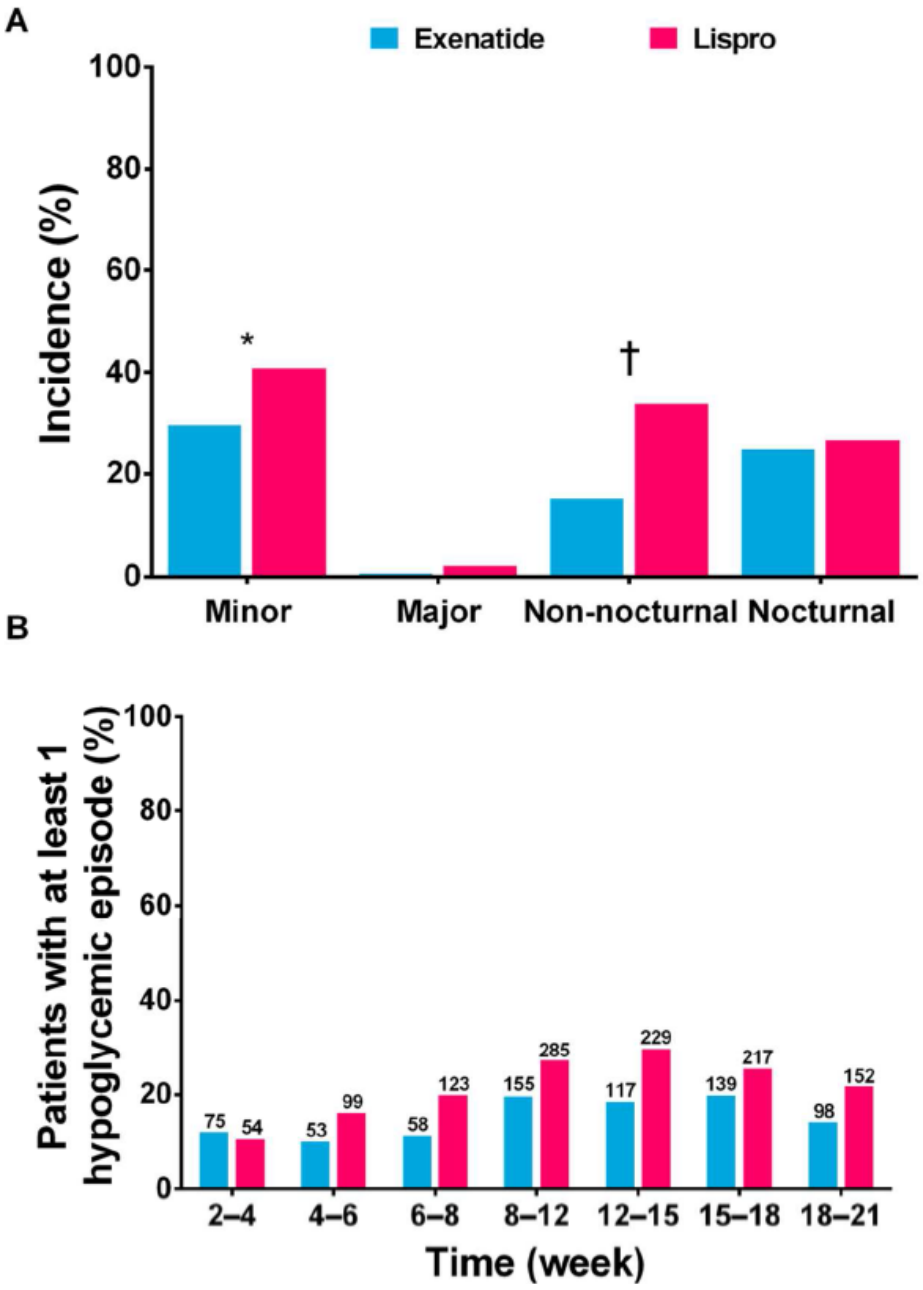
Supplementary Figure 3. Hypoglycemia



Panel A shows incidence of hypoglycemia in the as-treated population (N=627). The incidence was significantly different between the exenatide and lispro groups for minor (*p=0.004) and non-nocturnal (†p<0.001) hypoglycemia.
Panel B shows the percentage of patients with symptoms of hypoglycemia in the as-treated population, and the number of hypoglycemic episodes during the course of the study.

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Supplement Figure 4. Anti-exenatide antibody status