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## ONLINE-ONLY SUPPLEMENTAL MATERIAL

### Additional Acknowledgments

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The study was performed at 27 study centers in 6 countries. Twenty-seven study centers randomized participants during the study.

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## METHODS

### Selection of Study Population

#### *Full Inclusion Criteria*

For inclusion in the study, potential participants had to fulfill all of the following criteria:

1. Was a child or an adolescent aged 10 to <18 years at visit 1 (screening)
2. Had been diagnosed with type 2 diabetes per the American Diabetes Association diagnostic criteria
3. Had a glycated hemoglobin level of 6.5% (48 mmol/mol) to 11.0% (97 mmol/mol), inclusive, for participants not taking insulin/sulfonylurea, and of 6.5% (48 mmol/mol) to 12.0% (108 mmol/mol), inclusive, for participants taking insulin/sulfonylurea at visit 1 (screening)
4. Had a C-peptide of >0.6 ng/mL at visit 1 (screening)
5. Had been treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (e.g., metformin and/or a sulfonylurea) and/or insulin for type 2 diabetes for at least 2 months prior to visit 1 (screening)
6. Had a fasting plasma glucose level of <280 mg/dL (15.5 mmol/L) at visit 1 (screening)
7. Either was not treated with or had been on a stable treatment regimen with any of the following medications for a minimum of 1 month prior to visit 1 (screening):
  - a) Oral contraceptives (female participants)
  - b) Antihypertensive agents
  - c) Lipid-lowering agents
  - d) Thyroid replacement therapy
  - e) Antidepressant agents
8. Was male, or was female and met all the following criteria:

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- a) Not breastfeeding
  - b) Negative serum pregnancy test result (human chorionic gonadotropin, beta subunit [ $\beta$ hCG]) at visit 1 (screening)
  - c) If of childbearing potential, was to practice and be willing to continue to practice appropriate birth control (defined as at least 1 method resulting in a low failure rate, that is, less than 1% per year, when used consistently and correctly, such as implants, injectables, hormonal contraceptives, some intrauterine contraceptive devices, sexual abstinence, tubal ligation or occlusion, or a vasectomized partner) during the entire duration of the study and must not have been planning to conceive
- 9. Had clinical laboratory test values (clinical chemistry, hematology, and urinalysis) judged as not being clinically significant by the investigator at visit 1 (screening)
  - 10. Had physical examination and electrocardiogram (ECG) results deemed not clinically significant by the investigator at visit 2 (week 0)
  - 11. Both participant and parent/caretaker were able to read, understand, and sign the informed consent form and Child Assent Form and, if applicable, an Authorization to Use and Disclose Protected Health Information form (consistent with the United States Health Insurance Portability and Accountability Act legislation); communicate with the investigator; and understand and comply with protocol requirements
  - 12. Both participant and parent/caretaker were able to read and understand the lifestyle modification program, and the parent/caretaker was willing to assist the participant to adhere to the lifestyle modification program

#### *Full Exclusion Criteria*

Potential participants were not to enter the study if any of the following exclusion criteria was met:

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1. Had a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the investigator, including but not limited to the following conditions:
    - a) Hepatic disease (defined as aspartate or alanine transaminase  $>3.0 \times$  upper limit of normal [ULN])
    - b) Renal disease or serum creatinine  $>1.5$  mg/dL (132.6  $\mu$ mol/L; in males) or 1.4 mg/dL (123.8  $\mu$ mol/L; in females)
    - c) Gastrointestinal disease deemed significant by the investigator
    - d) Organ transplantation
    - e) Chronic infection (e.g., tuberculosis, human immunodeficiency virus, hepatitis B virus, or hepatitis C virus)
    - f) Clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of visit 1 (screening)
  2. Had positive antibody titers to glutamic acid decarboxylase (GAD65) or islet cell antigen (ICA512) at visit 1 (screening)
  3. Had a personal or family history of elevated calcitonin, calcitonin  $>100$  ng/L, medullary thyroid carcinoma, or multiple endocrine neoplasia-2
  4. Had donated blood within 2 months of visit 1 (screening), was planning to donate blood during the study, or had a hematocrit of  $<30\%$
  5. Had undergone a major surgery or a blood transfusion within 2 months of visit 1 (screening)
  6. Had received any investigational drug within 1 month (or 5 half-lives of the investigational drug, whichever is greater) of visit 1 (screening)
  7. Had ever used exenatide (exenatide twice daily or any other formulation) or any glucagon-like peptide-1 receptor agonist (e.g., liraglutide)

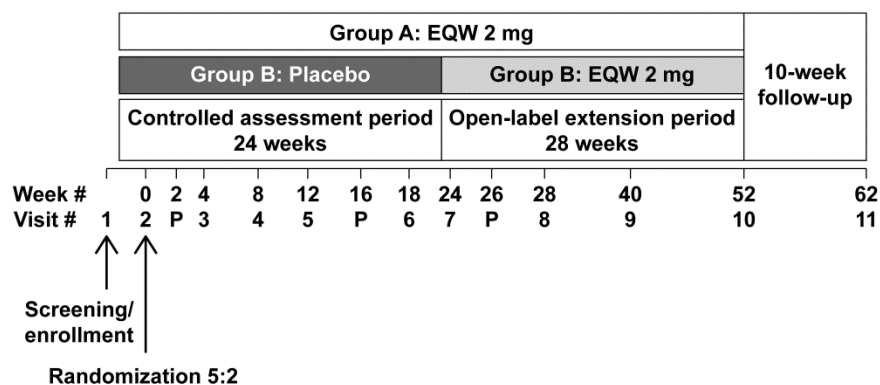
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8. Was a current abuser of drugs and/or alcohol or had a history of abuse that in the investigator's opinion would cause the individual to be noncompliant with the study procedures
  9. Had known allergies or hypersensitivity to any component of the study treatment (including poly D,L-lactide-co-glycolide and microsphere diluent)
  10. Had been treated, was currently being treated, or was expected to require or undergo treatment with any of the following medications:
    - a) Oral glucocorticoids or corticosteroids within the last 30 days or more than 20 days within the past year. However, glucocorticoid treatment for some infections for less than 10 days was allowed
    - b) Thiazolidinedione within 90 days prior to visit 1 (screening)
    - c) Inhaled glucocorticoids at a dose equal to or above 1000 µg FLOVENT® (fluticasone propionate) daily
    - d) Weight loss medication(s) (including over-the-counter medications) within 30 days of visit 1 (screening)
    - e) Alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide for >1 week in the 1 month prior to visit 1 (screening)
    - f) Dipeptidyl peptidase-4 inhibitors within 30 days prior to visit 1 (screening)
  11. Had admitted use of anabolic steroids within the past 60 days or was planning use during the study
  12. Was an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the clinical study site, or was directly affiliated with the study at the clinical study site
  13. Was pregnant

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14. Was employed by AstraZeneca (i.e., an employee, temporary contract worker, or designee responsible for the conduct of the study)



## Supplemental Figure S1. Study design



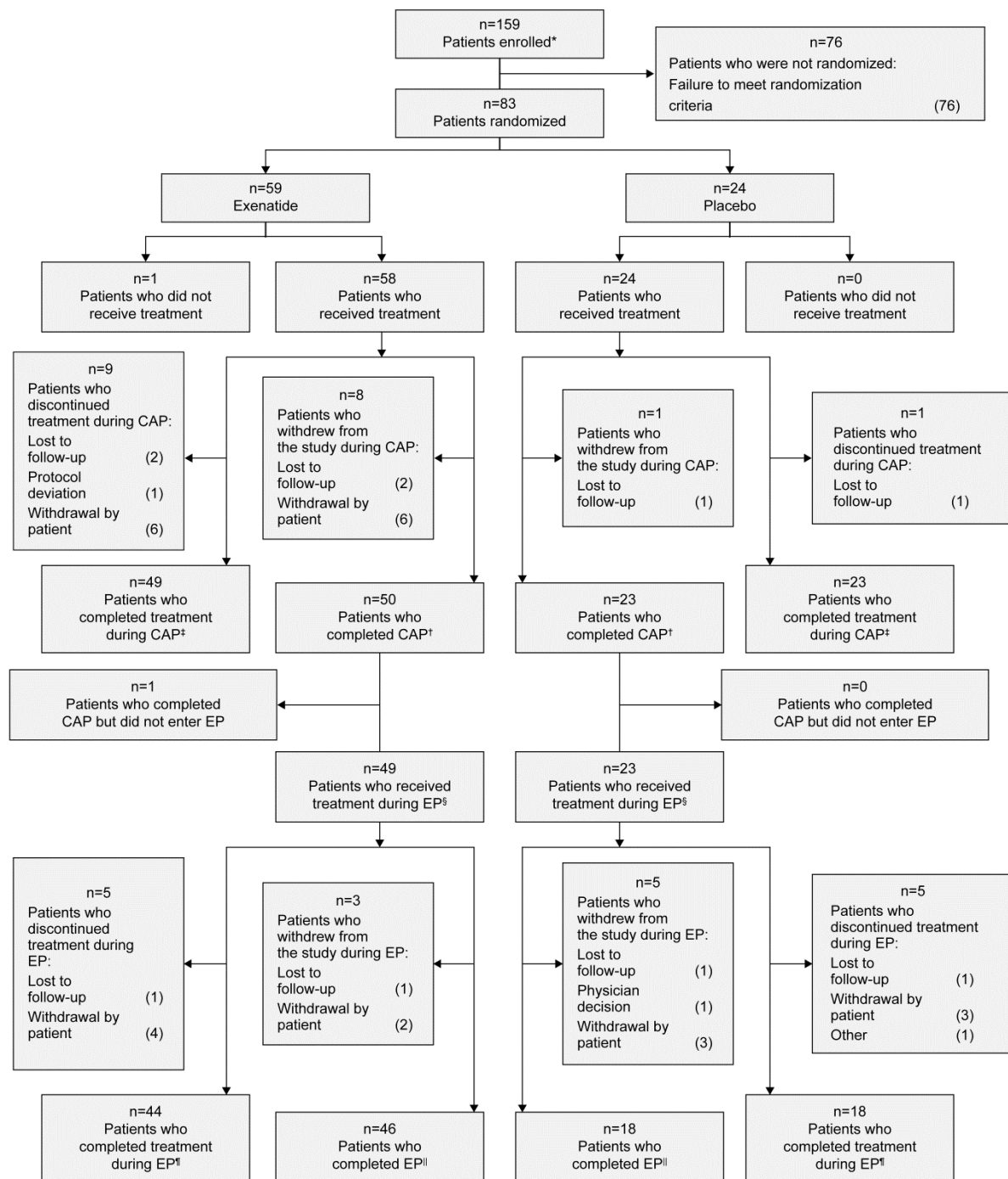
All visits scheduled during the controlled assessment period and during the open-label extension period were to occur within  $\pm 2$  days of the scheduled date, relative to Visit 2 (Week 0).

Visit 11 was to take place at least 10 weeks and no later than 12 weeks after the last dose of EQW.

The Investigator and/or qualified study-site personnel were to contact patients by phone at Week 2, Week 16, and Week 26 to discuss study compliance, address any questions related to study medication, and review AEs.

AE Adverse event; EQW Exenatide once weekly; P Phone call.

## Supplemental Figure S2. Participant disposition



\*Informed consent/assent received.

†Patients who received at least 1 dose of study medication, did not prematurely withdraw from the study prior to week 24, and had a week 24 assessment regardless of randomized treatment status at the visit.

‡Patients who did not prematurely discontinue exenatide/placebo prior to week 24.

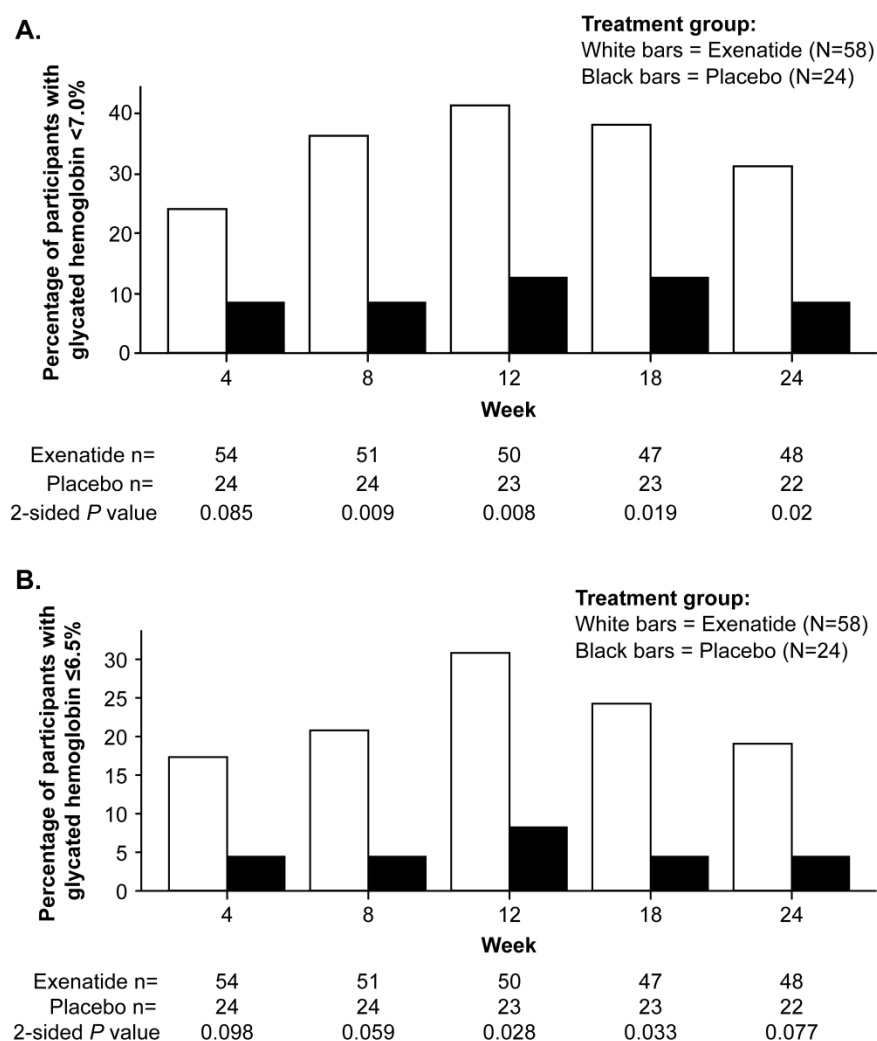
§All patients who completed the controlled assessment period and received open-label exenatide during the extension period.

¶Patients who did not prematurely withdraw from the study prior to week 52.

||Patients who did not prematurely discontinue exenatide prior to week 52.

CAP, controlled assessment period; EP, extension period.

Supplemental Figure S3. Proportions of participants meeting the glycated hemoglobin level of (A) <7% or (B) ≤6.5% at week 24 and at each intermediate visit



All participants with missing endpoint data were imputed as nonresponders. The treatment group comparison was based on a Cochran-Mantel-Haenszel test stratified by the screening glycated hemoglobin (<9.0% or ≥9.0%). The *P* values were obtained from the general association statistics. Data collected on or after the initiation of rescue medication or after premature discontinuation of the study medication were excluded.

Supplemental Table S1. Observed values and changes in lipid profiles from baseline to week 24 (intention-to-treat analysis set)

Treatment group	Analysis visit	n	Mean	SD	Min	Median	Max
P-cholesterol, fasting (mmol/L)							
Exenatide (N=58)	Baseline	57	4.33	1.10	2.82	4.09	8.51
	Week 24	47	4.25	0.98	2.61	4.20	7.10
Placebo (N=24)	Baseline	23	4.46	0.93	2.77	4.47	6.49
	Week 24	22	4.39	0.69	3.23	4.28	6.13
Change from baseline							
Exenatide (N=58)	Week 24	46	-0.12	0.71	-3.03	-0.07	1.16
Placebo (N=24)	Week 24	21	-0.11	0.58	-1.66	0.00	0.78
S-HDL-cholesterol, fasting (mmol/L)							
Exenatide (N=58)	Baseline	57	1.08	0.33	0.52	0.98	2.15
	Week 24	47	1.07	0.28	0.57	1.03	1.63
Placebo (N=24)	Baseline	23	1.12	0.26	0.65	1.11	1.86
	Week 24	22	1.07	0.25	0.65	1.06	1.79
Change from baseline							
Exenatide (N=58)	Week 24	46	-0.04	0.20	-0.70	-0.03	0.36
Placebo (N=24)	Week 24	21	-0.05	0.10	-0.28	-0.05	0.10
S-LDL-cholesterol, calculated, fasting (mmol/L)							

Exenatide	Baseline	54	2.45	0.95	1.11	2.13	5.69
(N=58)	Week	46	2.46	0.83	1.01	2.30	5.34
	24						
<b>Placebo</b>	Baseline	23	2.58	0.83	1.11	2.59	4.45
<b>(N=24)</b>	Week	21	2.53	0.64	1.81	2.38	4.50
	24						
Change from baseline							
Exenatide	Week	43	-0.05	0.56	-2.28	0.00	1.01
(N=58)	24						
Placebo	Week	20	-0.11	0.60	-1.78	0.05	0.70
(N=24)	24						
S-triglycerides, fasting (mmol/L)							
Exenatide	Baseline	57	1.82	1.18	0.44	1.43	6.28
(N=58)	Week	47	1.65	1.05	0.50	1.26	5.33
	24						
Placebo	Baseline	23	1.66	0.79	0.56	1.39	3.25
(N=24)	Week	22	1.77	1.02	0.51	1.58	4.99
	24						
Change from baseline							
Exenatide	Week	46	-0.12	1.03	-4.70	-0.13	2.46
(N=58)	24						
Placebo	Week	21	0.09	0.66	-1.40	0.10	1.74
(N=24)	24						

Samples for all lipid parameters presented were collected in a fasted state.

Baseline was defined as the last nonmissing assessment (scheduled or unscheduled) on or prior to the first dose of the randomized study medication.

Data collected after the initiation of rescue medication or after premature discontinuation of the study medication were excluded.

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HDL, high-density lipoprotein; LDL, low-density lipoprotein; max, maximum; min, minimum; N, number of participants in the intention-to-treat analysis set within the treatment group; n, number of participants included in analysis; P, plasma; S, serum; SD, standard deviation.

Supplemental Table S2. Incidence of hypoglycemia by ADA classification (16, 17)

(controlled assessment period; safety analysis set)

	Exenatide (N=59)		Placebo (N=23)	
	Number (%) of participants	Number of events	Number (%) of participants	Number of events
Level 1 <sup>*</sup>	4 (6.8)	8	1 (4.3)	7
Level 2 <sup>†</sup>	2 (3.4)	2	1 (4.3)	1
Level 3 <sup>‡</sup>	1 <sup>§</sup> (1.7)	1	0	0

<sup>\*</sup>Glucose level of  $\leq 3.9$  mmol/L (70 mg/dL).

<sup>†</sup>Glucose level of  $< 3.0$  mmol/L (54 mg/dL).

<sup>‡</sup>Severe hypoglycemia, defined as severe cognitive impairment requiring external assistance for recovery.

<sup>§</sup>One participant was defined as having a level 3 hypoglycemia after programmatically applying the definitions to the available data set. This was a 15-year-old male who experienced an event of level 3 hypoglycemia 17 days into the study, which was severe in intensity. The participant was not receiving concomitant insulin or sulfonylurea. The event was symptomatic and occurred while the participant was awake, with a reported duration of 8 hours. Reported symptoms were confusion, dizziness/light-headedness, drowsiness, hunger, and feeling shaky. The participant had a fingerstick glucose value of 4.66 mmol/L (84 mg/dL). His HbA1c at baseline was 8.9%. A reported potential cause for this event was fasting for 10 hours prior to sedation for a medical test. The participant received third party assistance but the type of assistance given was not documented.

Participants with multiple hypoglycemia events in a single category are counted only once. Multiple hypoglycemic events for a participant are considered in the total event calculation.

ADA, American Diabetes Association.

Supplemental Table S3. Incidence of hypoglycemia in participants using insulin and/or a sulfonylurea at baseline (controlled assessment period; safety analysis set)

Baseline insulin/ sulfonylurea use	Exenatide (N=59)		Placebo (N=23)	
	Number of participants included	Number of participants with any event of hypoglycemia	Number of participants included	Number of participants with any event of hypoglycemia
Any*	59	8 (13.6)	23	1 (4.3)
Insulin and sulfonylurea	0	0	0	0
Insulin only	27	6 (22.2)	11	1 (9.1)
Sulfonylurea only	1	0	0	0
No insulin or sulfonylurea	31	2 (6.5)	12	0

\*Included all participants regardless of baseline insulin and sulfonylurea use. Participants with no insulin or sulfonylurea use at baseline were included.

A controlled assessment period event was defined as an event starting on or after the day of the first dose of the study medication up to but not including week 24 for participants entering the extension period. For participants not entering the extension period, the period was defined up to and including the last dose of the study medication +7 days.

Baseline use was defined as medication received on the day before the date of the first dose of the randomized study medication.

For participants completing the controlled assessment period treatment but not entering the extension period, events were captured up to the later of the date of the last dose + 7 days, or week 24.

Hypoglycemia events reported from the hypoglycemic event eCRF.

Percentages were calculated from the number of participants included in each category by treatment group.



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eCRF, electronic case report form; N, number of participants in the treatment group.