## Supporting Information

### Analysis populations

The modified intention-to-treat (mITT) population—the primary analysis population containing all randomized patients who received at least one dose of study drug—was used for efficacy and pharmacodynamic analyses. The treated population consisted of all patients who received at least one dose of study drug, including patients who received study medication but were not randomized. The treated population was used for safety analyses. The week 28-evaluable population consisted of all patients in the mITT population who completed the study through week 24 (the visit before the week 28 visit). The meal test-evaluable population consisted of patients in the mITT population who participated in the meal test, consumed at least 75% of the standardized meal, and did not have missing 2-hour postprandial glucose measurements at baseline, day 1, and week 16. Finally, the pharmacokinetics-evaluable population comprised all patients in the mITT population who had adequate and reliable pharmacokinetics data.

### Models used for analysis

For the mixed-effects model for repeated measures (MMRM), treatment, diabetes management method at screening, renal function, visit week, treatment-by-visit interaction, and glycated hemoglobin (HbA1c) stratum (<9.0% or ≥9.0% [<75 or ≥75 mmol/mol]) at screening were included as fixed factors, patient was included as a random effect, and the baseline value of the parameter analyzed was included as a covariate. A treatment-by-sex, treatment-by-age (<65 and ≥65 years), or treatment-by-race interaction was explored separately with an MMRM, with additional covariates of subgroups (sex, age, or race), treatment by subgroup, week by subgroup,

and treatment by week by subgroup. The Cochran-Mantel-Haenszel test was stratified by HbA1c stratum at screening, diabetes management method, and renal function.

**Compliance**

Compliance was measured as the percentage of injections received relative to the number of planned injections and was high for both groups (mean ± standard deviation: 90.0 ± 22.0% with exenatide once-weekly suspension by autoinjector [QWS-AI]; 83.7 ± 29.6% with exenatide twice daily [BID]) during the 28-week controlled period. Likewise, when compliance was measured during the time between the first and last dose (rather than across the study period), the mean ± standard deviation percentage of study medication injections received compared with study medication injections planned was 98.6 ± 5.3% for exenatide QWS-AI and 96.4 ± 8.3% for exenatide BID.

**TABLE S1** Changes in $iAUC_{(0–5h)}$ postprandial serum insulin and triglycerides (meal test-evaluable population)

| | **Exenatide QWS-AI (n=31)** | **Exenatide BID (n=37)** |
|---|---|---|
| Insulin $iAUC_{(0–5h)}$, mU.h/L | | |
| Baseline, mean ± SE | 162.0 ± 26.4 | 127.1 ± 11.6 |
| LSM ± SE change from baseline to week 16 | +24.0 ± 28.2 | −59.9 ± 31.6 |
| LSM ± SE difference vs exenatide BID | 83.9 ± 33.2 | — |
| p value | 0.0142 | — |
| Triglyceride $iAUC_{(0–5h)}$, mmol.h/L | | |
| Baseline, mean ± SE | 1.7 ± 0.3 | 1.7 ± 0.3 |
| LSM ± SE change from baseline to week 16 | −0.1 ± 0.4 | −1.2 ± 0.4 |
| LSM ± SE difference vs exenatide BID | 1.0 ± 0.5 | — |
| p value | 0.0293 | — |

BID, twice daily; $iAUC_{(0–5h)}$, incremental area under the curve from 0–5 hours; LSM, least-squares mean; QWS-AI, once-weekly suspension by autoinjector; SE, standard error.

**TABLE S2** Changes in cardiovascular risk factors (modified intention-to-treat population)

| | **Exenatide QWS-AI (n=229)** | **Exenatide BID (n=146)** |
|---|---|---|
| Systolic BP, mm Hg | | |
| Baseline | 129.8 ± 1.0 | 130.3 ± 1.2 |
| Change from baseline to week 28 | −0.8 ± 1.1 | −1.6 ± 1.4 |
| Diastolic BP, mm Hg | | |
| Baseline | 78.2 ± 0.6 | 80.0 ± 0.7 |
| Change from baseline to week 28 | +0.2 ± 0.6* | −1.9 ± 0.8 |
| Heart rate, beats/min | | |
| Baseline, mean ± SD | 75.1 ± 11.1 | 74.0 ± 10.4 |
| Change from baseline to week 28, mean ± SD | +1.9 ± 9.4 | +1.6 ± 8.5 |
| Total cholesterol, mmol/L | | |
| Baseline | 4.7 ± 0.09 | 4.5 ± 0.09 |
| Change from baseline to week 28 | −0.1 ± 0.06 | −0.1 ± 0.07 |
| 95% CI | −0.2; 0.0 | −0.2; +0.1 |
| HDL cholesterol, mmol/L | | |
| Baseline | 1.2 ± 0.02 | 1.1 ± 0.03 |
| Change from baseline to week 28 | 0.0 ± 0.02 | 0.0 ± 0.02 |
| 95% CI | 0.0; 0.0 | 0.0; +0.1 |

| | **Exenatide QWS-AI (n=229)** | **Exenatide BID (n=146)** |
|---|---|---|
| LDL cholesterol, mmol/L | | |
| Baseline | 2.6 ± 0.07 | 2.5 ± 0.08 |
| Change from baseline to week 28 | −0.2 ± 0.05 | −0.1 ± 0.06 |
| 95% CI | −0.2; –0.1 | −0.2; 0.0 |
| Triglycerides, mmol/L | | |
| Baseline, geometric mean ± SE | 1.9 ± 0.06 | 1.8 ± 0.07 |
| Ratio of week 28 to baseline, geometric LS mean ± SE | 1.0 ± 0.03 | 1.0 ± 0.04 |
| Geometric 95% CI | 1.0; 1.1 | 0.9; 1.1 |

Data are LS mean ± SE unless otherwise stated.

BID, twice daily; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least-squares; QWS-AI, once-weekly suspension by autoinjector; SD, standard deviation; SE, standard error.

*p<0.05 vs exenatide BID.

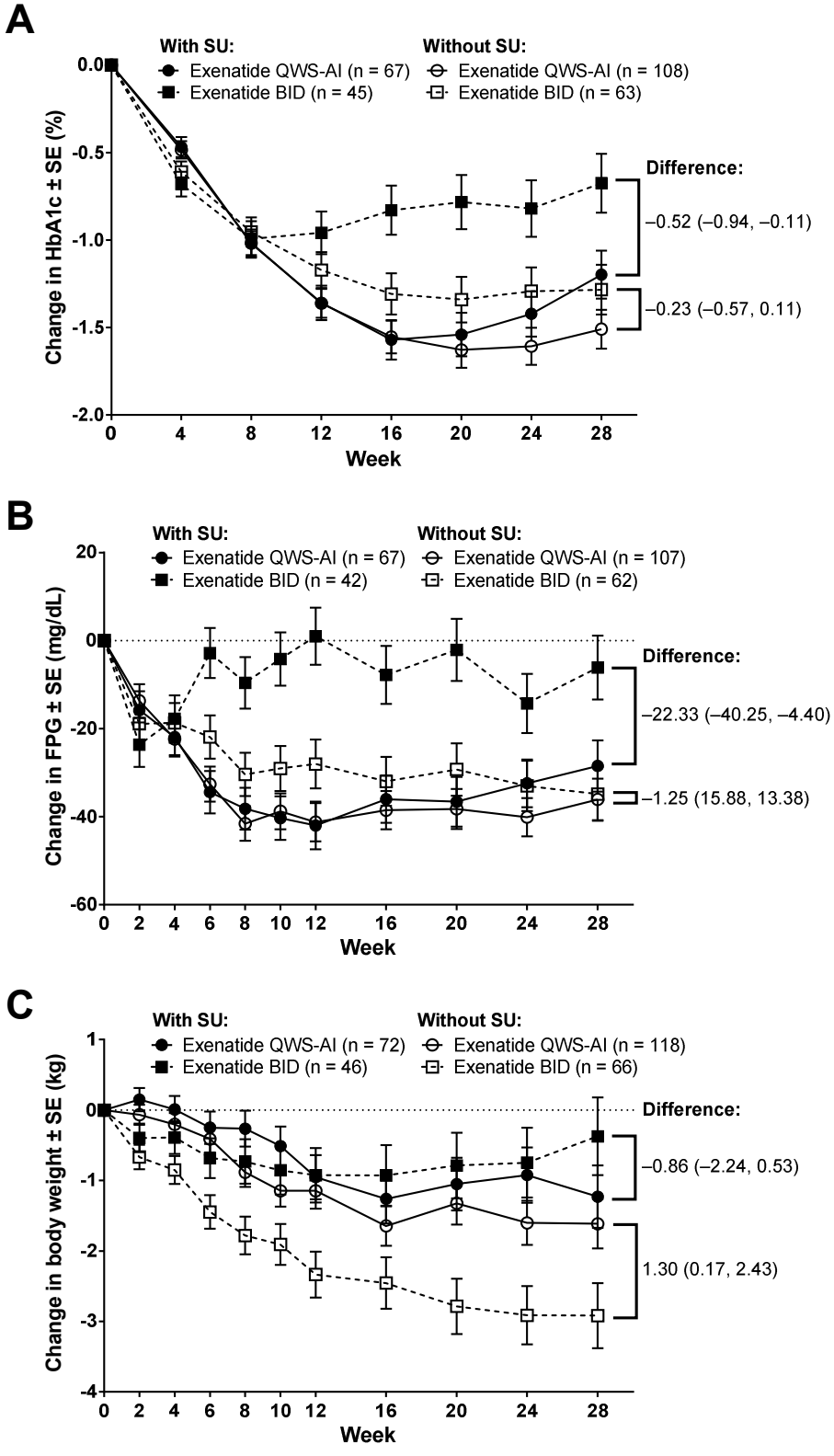
**TABLE S3** Change in HbA1c from baseline to week 28 by treatment-emergent antibody status (modified intention-to-treat population)

| **Antibody status** | **Exenatide QWS-AI (n=229)** | **Exenatide BID (n=146)** |
|---|---|---|
| Negative | | |
| n | 101 | 104 |
| LOCF change in HbA1c, % | −1.39 ± 1.11 | −1.07 ± 1.08 |
| Low-positive (<625) | | |
| n | 94 | 33 |
| LOCF change in HbA1c, % | −1.48 ± 1.25 | −0.93 ± 1.44 |
| High-positive (≥625) | | |
| n | 31 | 6 |
| LOCF change in HbA1c, % | −0.74 ± 1.33 | 0.05 ± 0.47 |

Data are mean ± standard deviation and are based on the number of patients with available antibody status and HbA1c results.

BID, twice daily; HbA1c, glycated hemoglobin; LOCF, last observation carried forward; QWS-AI, once-weekly suspension by autoinjector.

**FIGURE S1** Change in (A) HbA1c, (B) FPG, and (C) body weight over time for patients in the modified intention-to-treat population based on SU use. Differences are exenatide QWS-AI – exenatide BID (95% confidence interval). BID, twice daily; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; QWS-AI, once-weekly suspension by autoinjector; SE, standard error; SU, sulfonylurea.


A
With SU:
Exenatide QWS-AI (n = 67)
Exenatide BID (n = 45)
Without SU:
Exenatide QWS-AI (n = 108)
Exenatide BID (n = 63)
Change in HbA1c ± SE (%)
0.0
-0.5
-1.0
-1.5
-2.0
0
4
8
12
16
20
24
28
Week
Difference:
–0.52 (–0.94, –0.11)
–0.23 (–0.57, 0.11)
B
With SU:
Exenatide QWS-AI (n = 67)
Exenatide BID (n = 42)
Without SU:
Exenatide QWS-AI (n = 107)
Exenatide BID (n = 62)
Change in FPG ± SE (mg/dL)
20
0
-20
-40
-60
0
2
4
6
8
10
12
16
20
24
28
Week
Difference:
–22.33 (–40.25, –4.40)
–1.25 (15.88, 13.38)
C
With SU:
Exenatide QWS-AI (n = 72)
Exenatide BID (n = 46)
Without SU:
Exenatide QWS-AI (n = 118)
Exenatide BID (n = 66)
Change in body weight ± SE (kg)
1
0
-1
-2
-3
-4
0
2
4
6
8
10
12
16
20
24
28
Week
Difference:
–0.86 (–2.24, 0.53)
1.30 (0.17, 2.43)

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