**Supplementary Figure 1.** Patient disposition.

- **Patients screened** (N=1374)
- **Patients randomized** (N=680)
  - Lixisenatide morning injection (N=255)
    - Discontinuations at week 24
      - Adverse event, 12 (4.7%)
      - Lack of efficacy, 1 (0.4%)
      - Poor protocol compliance, 2 (0.8%)
      - Lost to follow up, 1 (0.4%)
      - Other reasons, 6 (2.4%)
    - Completed 91.4% (N=233)
  - Lixisenatide evening injection (N=255)
    - Discontinuations at week 24
      - Adverse event, 13 (5.1%)
      - Lack of efficacy, 0
      - Poor protocol compliance, 7 (2.7%)
      - Lost to follow up, 0
      - Other reasons, 11 (4.3%)
    - Completed 87.6% (N=224)
  - Placebo (N=170)
    - Discontinuations at week 24
      - Adverse event, 2 (1.2%)
      - Lack of efficacy, 3 (1.8%)
      - Poor protocol compliance, 3 (1.8%)
      - Lost to follow up, 0
      - Other reasons, 4 (2.4%)
    - Completed 92.9% (N=158)
**Supplementary Figure 2.** Effect on HOMA-B at Week 24 with lixisenatide morning once-daily regimen, lixisenatide evening once-daily regimen and placebo. Data are LS mean (± SE) change from baseline. Mean (± SD) baseline HOMA-B values were 43.0 (33.2) (lixisenatide morning; n=255), 45.5 (42.8) (lixisenatide evening; n=255) and 41.7 (42.9) (placebo combined; n=170). LS mean difference (± SE) versus placebo at Week 24: 12.1 (3.28) [95% CI: 5.69, 18.56], p=0.0002 (morning) and 9.0 [95% CI: 2.45, 15.48], p=0.0071 (evening).

HOMA-B= homeostasis model assessment-B; LS=least squares; SE=standard error; SD=standard deviation.