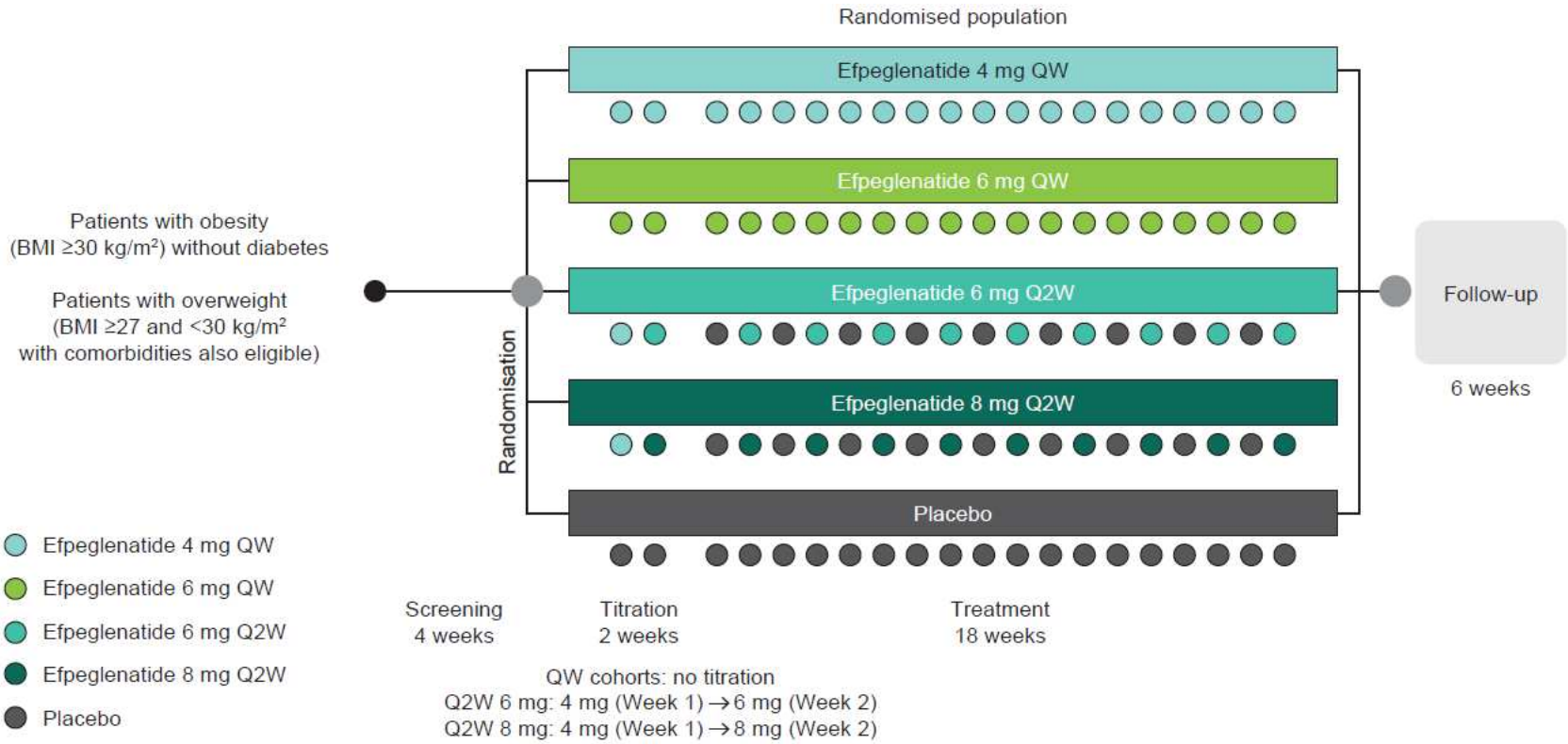
# Supplementary Material

**Supplementary Figure S1 BALANCE study design**

*BMI* body mass index, *QW* once weekly, *Q2W* once every 2 weeks

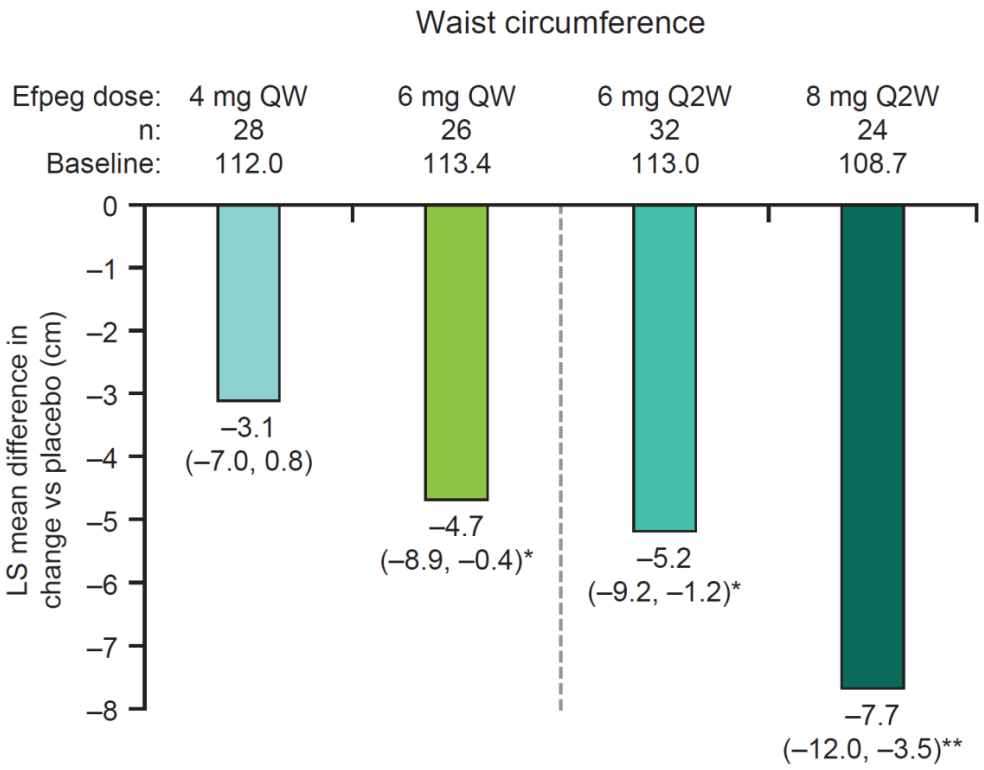


**Supplementary Figure S2 Patients with prediabetes: change from baseline to Week 21 versus placebo in waist circumference**

95.1% CI data are shown in brackets

*CI confidence interval, Efpeg* efpeglenatide, *LS* least square, *QW* once weekly, *Q2W* once every 2 weeks

**p*<0.05; ***p*<0.01

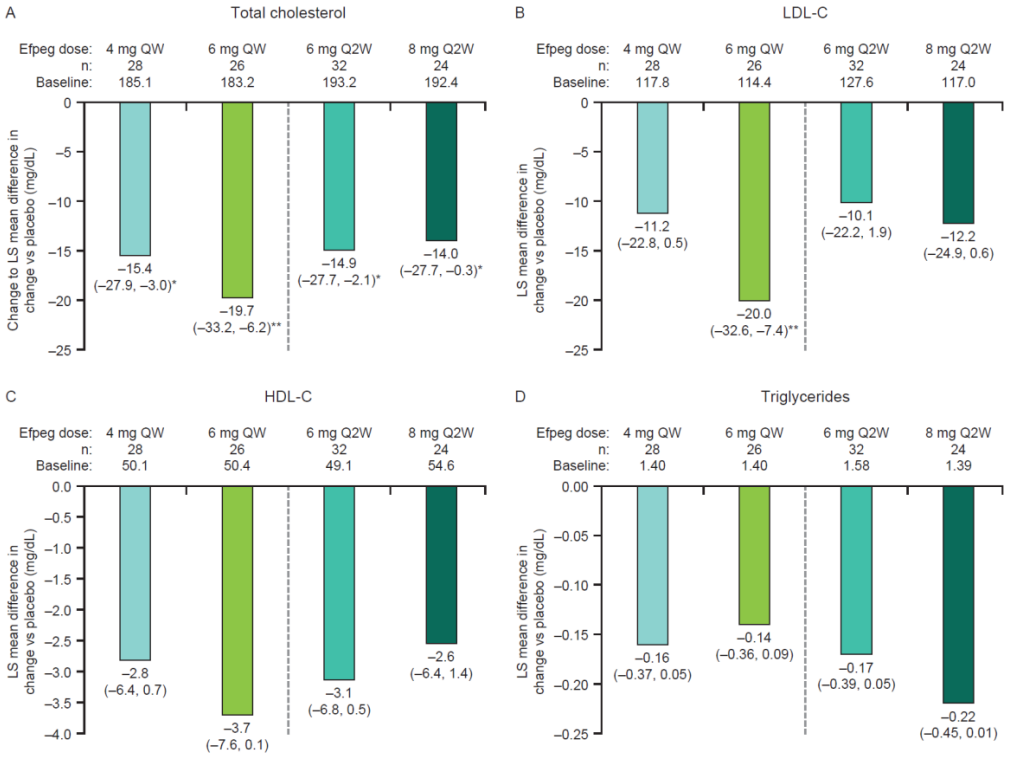


**Supplementary Figure S3 Patients with prediabetes: change from baseline to Week 21 versus placebo in (a) total cholesterol, (b) LDL-C, (c) HDL-C, and (d) triglycerides**

95.1% CI data are shown in brackets

*CI confidence interval, Efpeg* efpeglenatide, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LS* least square, *QW* once weekly, *Q2W* once every 2 weeks

**p*<0.05; ***p*<0.01



17 **Supplementary Table S1 Details of ethics review boards**

| Country | Review board | Local/Central | ID |
|---|---|---|---|
| Germany | CRC Hanover* | Central | 6619M |
| Germany | Landesamt für Gesundheit und Soziales Berlin, Geschäftsstelle der Ethik-Kommission des Landes Berlin | Local | – |
| Germany | Ethikkommission bei der Sachsischen Landesärztekammer | Local | – |
| Germany | Ethikkommission der Landesärztekammer Baden-Württemberg | Local | – |
| Germany | Ethikkommission der Äerztekammer Nordrhein | Local | – |
| Hungary | Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsága | Central | OGYI/2370-8/2014 |
| Netherlands | METC BRABANT | Central | P1404 |
| South Korea | Inje University Seoul Paik Hospital | Local | SIT-2014-032 |
| South Korea | Kyung Hee University Hospital at Gangdong | Local | KHNMC 2014-02-005-023 |
| South Korea | Korea University Guro Hospital | Local | KUGH13283-024 |
| South Korea | Chungnam National University Hospital | Local | CNUH 2014-02-005-023 |
| South Korea | Bucheon St. Mary's Hospital | Local | HC14MGGS0023 |
| South Korea | Asan Medical Center | Local | 2014-0362 |
| South Korea | Konkuk University Medical Center | Local | KUH1230016 |
| U.S. | Quorum Review Institutional Review Board | Central | 28889 |

18 *The CRC Hanover review board replaced the local review boards in Germany and local IRB numbers are not available.

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**Supplementary Table S2 Patients with prediabetes: key treatment-emergent adverse events (full analysis set)**

| Treatment-emergent AEs, n (%)[a] | Efpeglenatide | | | | |
|---|---|---|---|---|---|
| | 4 mg QW (n=28) | 6 mg QW (n=26) | 6 mg Q2W (n=32) | 8 mg Q2W (n=24) | Placebo (n=30) |
| **Any TEAEs** | 24 (85.7) | 23 (88.5) | 31 (96.9) | 21 (87.5) | 24 (80.0) |
| **Any serious TEAEs** | 1 (3.6) | 2 (7.7) | 0 | 2 (8.3) | 0 |
| **Gastrointestinal disorders[b]** | 18 (64.3) | 20 (76.9) | 23 (71.9) | 17 (70.8) | 12 (40.0) |
| Nausea | 15 (53.6) | 12 (46.2) | 17 (53.1) | 11 (45.8) | 5 (16.7) |
| Vomiting | 4 (14.3) | 5 (19.2) | 7 (21.9) | 7 (29.2) | 3 (10.0) |
| Diarrhoea | 4 (14.3) | 3 (11.5) | 8 (25.0) | 4 (16.7) | 6 (20.0) |
| **Symptomatic hypoglycaemia[c]** | 0 | 1 (3.8) | 0 | 0 | 0 |

[a]Number of patients who reported at least one event; percentage calculated using subgroup n number as denominator; [b]Gastrointestinal TEAEs included nausea, vomiting, diarrhoea, dyspepsia and constipation; [c]Reported by patients in study diaries (with an alert value of FPG ≤70 mg/dL; no severe cases were reported [defined as hypoglycaemia requiring assistance from another person to administer carbohydrates or glucagon actively, or take other corrective actions])

*FPG* fasting plasma glucose, *QW* once weekly, *Q2W* once every 2 weeks, *TEAE* treatment-emergent adverse event

**Supplementary Table S3 Patients stratified by BMI and age at baseline: gastrointestinal treatment-emergent adverse events and amylase and lipase increases by subgroup (full analysis set)**

| | | Efpeglenatide | | | | |
|---|---|---|---|---|---|---|
| | | 4mg QW (n=59) | 6mg QW (n=59) | 6mg Q2W (n=59) | 8mg Q2W (n=58) | Placebo (n=60) |
| **BMI < or ≥ median** | | | | | | |
| GI disorders | BMI < Median | 24/32 (75.00%) | 22/23 (95.65%) | 20/28 (71.43%) | 24/32 (75.00%) | 14/31 (45.16%) |
| | BMI ≥ Median | 19/27 (70.37%) | 27/36 (75.00%) | 18/31 (58.06%) | 20/26 (76.92%) | 14/29 (48.28%) |
| Nausea | BMI < Median | 18/32 (56.25%) | 16/23 (69.57%) | 14/28 (50.00%) | 20/32 (62.50%) | 5/31 (16.13%) |
| | BMI ≥ Median | 14/27 (51.85%) | 19/36 (52.78%) | 14/31 (45.16%) | 16/26 (61.54%) | 6/29 (20.69%) |
| Vomiting | BMI < Median | 8/32 (25.00%) | 3/23 (13.04%) | 5/28 (17.86%) | 9/32 (28.13%) | 2/31 (6.45%) |
| | BMI ≥ Median | 5/27 (18.52%) | 10/36 (27.78%) | 5/31 (16.13%) | 10/26 (38.46%) | 2/29 (6.90%) |
| Diarrhoea | BMI < Median | 8/32 (25.00%) | 10/23 (43.48%) | 8/28 (28.57%) | 8/32 (25.00%) | 7/31 (22.58%) |
| | BMI ≥ Median | 6/27 (22.22%) | 2/36 (5.56%) | 7/31 (22.58%) | 8/26 (30.77%) | 5/29 (17.24%) |
| Dyspepsia | BMI < Median | 10/32 (31.25%) | 8/23 (34.78%) | 4/28 (14.29%) | 9/32 (28.13%) | 1/31 (3.23%) |
| | BMI ≥ Median | 2/27 (7.41%) | 8/36 (22.22%) | 5/31 (16.13%) | 6/26 (23.08%) | 1/29 (3.45%) |
| Constipation | BMI < Median | 7/32 (21.88%) | 4/23 (17.39%) | 6/28 (21.43%) | 8/32 (25.00%) | 3/31 (9.68%) |
| | BMI ≥ Median | 3/27 (11.11%) | 8/36 (22.22%) | 3/31 (9.68%) | 4/26 (15.38%) | 2/29 (6.90%) |

| | | Efpeglenatide | | | | |
|---|---|---|---|---|---|---|
| | | **4mg QW (n=59)** | **6mg QW (n=59)** | **6mg Q2W (n=59)** | **8mg Q2W (n=58)** | **Placebo (n=60)** |
| Lipase increased | BMI < Median | 3/32 (9.38%) | 1/23 (4.35%) | 0/28 (0.00%) | 3/32 (9.38%) | 2/31 (6.45%) |
| | BMI ≥ Median | 1/27 (3.70%) | 0/36 (0.00%) | 1/31 (3.23%) | 0/26 (0.00%) | 0/29 (0.00%) |
| Amylase increased | BMI < Median | 2/32 (6.25%) | 1/23 (4.35%) | 0/28 (0.00%) | 0/32 (0.00%) | 0/31 (0.00%) |
| | BMI ≥ Median | 0/27 (0.00%) | 0/36 (0.00%) | 0/31 (0.00%) | 0/26 (0.00%) | 0/29 (0.00%) |
| **Age < or ≥ median** | | | | | | |
| GI disorders | Age < Median | 19/28 (67.86%) | 25/31 (80.65%) | 18/28 (64.29%) | 16/28 (57.14%) | 13/28 (46.43%) |
| | Age ≥ Median | 24/31 (77.42%) | 24/28 (85.71%) | 20/31 (64.52%) | 28/30 (93.33%) | 15/32 (46.88%) |
| Nausea | Age < Median | 16/28 (57.14%) | 18/31 (58.06%) | 16/28 (57.14%) | 14/28 (50.00%) | 4/28 (14.29%) |
| | Age ≥ Median | 16/31 (51.61%) | 17/28 (60.71%) | 12/31 (38.71%) | 22/30 (73.33%) | 7/32 (21.88%) |
| Vomiting | Age < Median | 5/28 (17.86%) | 9/31 (29.03%) | 6/28 (21.43%) | 7/28 (25.00%) | 1/28 (3.57%) |
| | Age ≥ Median | 8/31 (25.81%) | 4/28 (14.29%) | 4/31 (12.90%) | 12/30 (40.00%) | 3/32 (9.38%) |
| Diarrhoea | Age < Median | 7/28 (25.00%) | 6/31 (19.35%) | 8/28 (28.57%) | 8/28 (28.57%) | 5/28 (17.86%) |
| | Age ≥ Median | 7/31 (22.58%) | 6/28 (21.43%) | 7/31 (22.58%) | 8/30 (26.67%) | 7/32 (21.88%) |
| Dyspepsia | Age < Median | 4/28 (14.29%) | 9/31 (29.03%) | 3/28 (10.71%) | 6/28 (21.43%) | 1/28 (3.57%) |
| | Age ≥ Median | 8/31 (25.81%) | 7/28 (25.00%) | 6/31 (19.35%) | 9/30 (30.00%) | 1/32 (3.13%) |

| | | Efpeglenatide | | | | |
|---|---|---|---|---|---|---|
| | | **4mg QW (n=59)** | **6mg QW (n=59)** | **6mg Q2W (n=59)** | **8mg Q2W (n=58)** | **Placebo (n=60)** |
| Constipation | Age < Median | 4/28 (14.29%) | 5/31 (16.13%) | 2/28 (7.14%) | 5/28 (17.86%) | 3/28 (10.71%) |
| | Age ≥ Median | 6/31 (19.35%) | 7/28 (25.00%) | 7/31 (22.58%) | 7/30 (23.33%) | 2/32 (6.25%) |
| Lipase increased | Age < Median | 2/28 (7.14%) | 1/31 (3.23%) | 1/28 (3.57%) | 0/28 (0.00%) | 1/28 (3.57%) |
| | Age ≥ Median | 2/31 (6.45%) | 0/28 (0.00%) | 0/31 (0.00%) | 3/30 (10.00%) | 1/32 (3.13%) |
| Amylase increased | Age < Median | 1/28 (3.57%) | 1/31 (3.23%) | 0/28 (0.00%) | 0/28 (0.00%) | 0/28 (0.00%) |
| | Age ≥ Median | 1/31 (3.23%) | 0/28 (0.00%) | 0/31 (0.00%) | 0/30 (0.00%) | 0/32 (0.00%) |

Median BMI=34.9 kg/$m^2$; median age=44 years

*BMI body mass index*, *GI* gastrointestinal, *QW* once weekly, *Q2W* once every 2 weeks