Supplemental material

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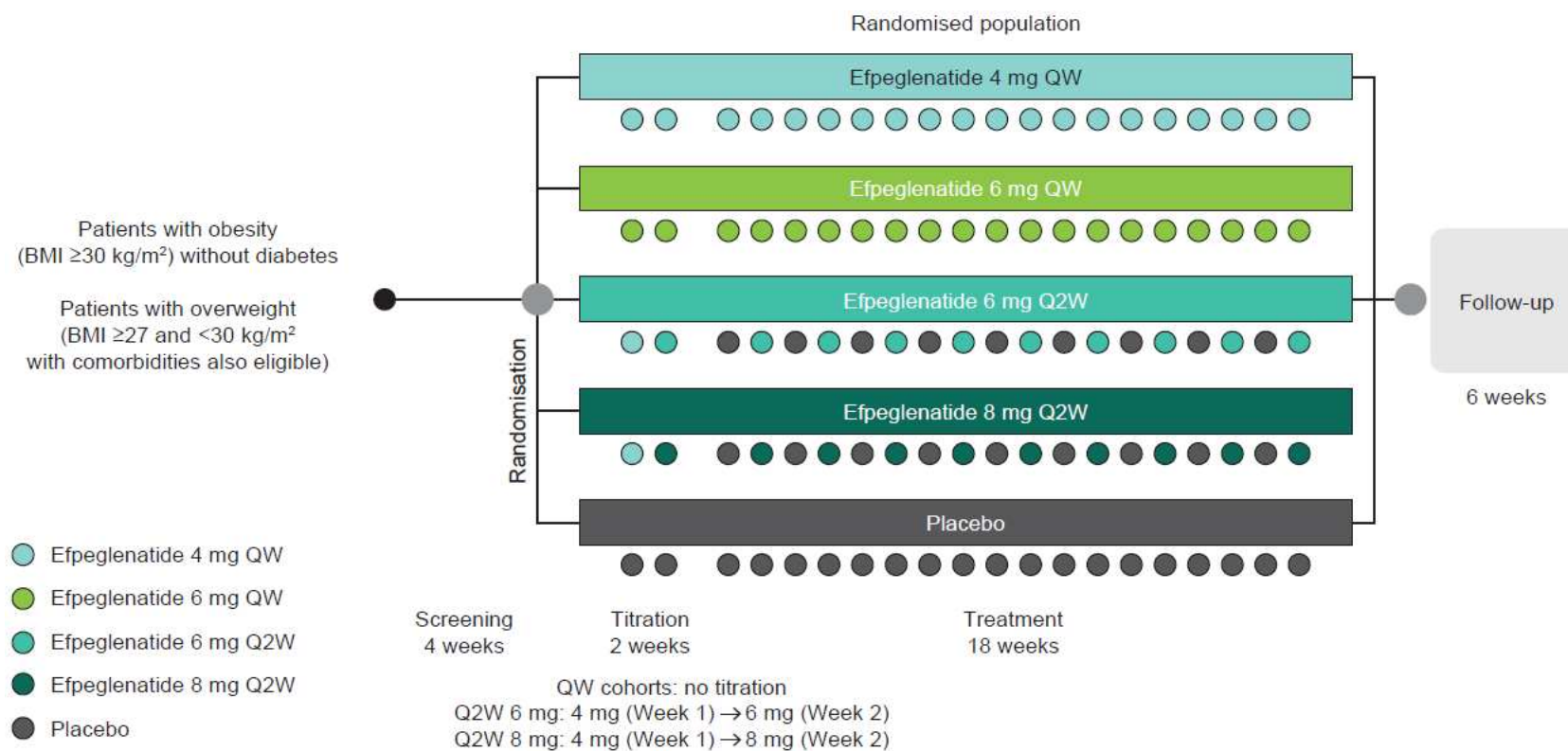*BMJ Open Diab Res Care*

1 **Supplementary Material**

2 **Supplementary Figure S1 BALANCE study design**

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

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Supplemental material

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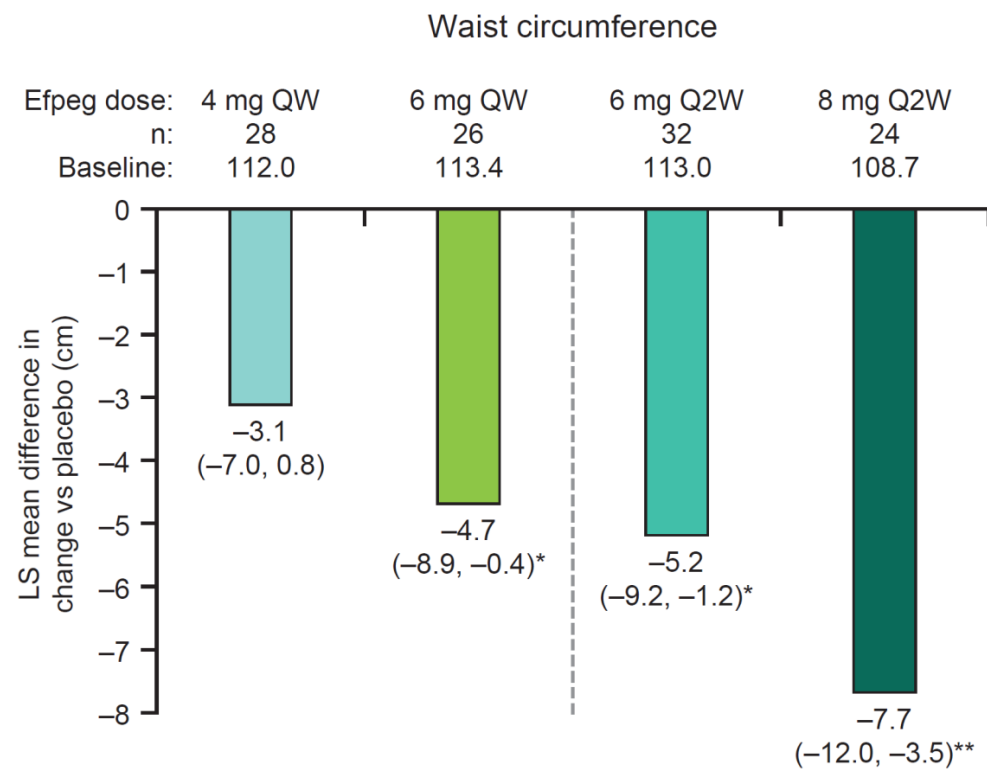
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5   **Supplementary Figure S2 Patients with prediabetes: change from baseline to Week 21 versus placebo in waist circumference**
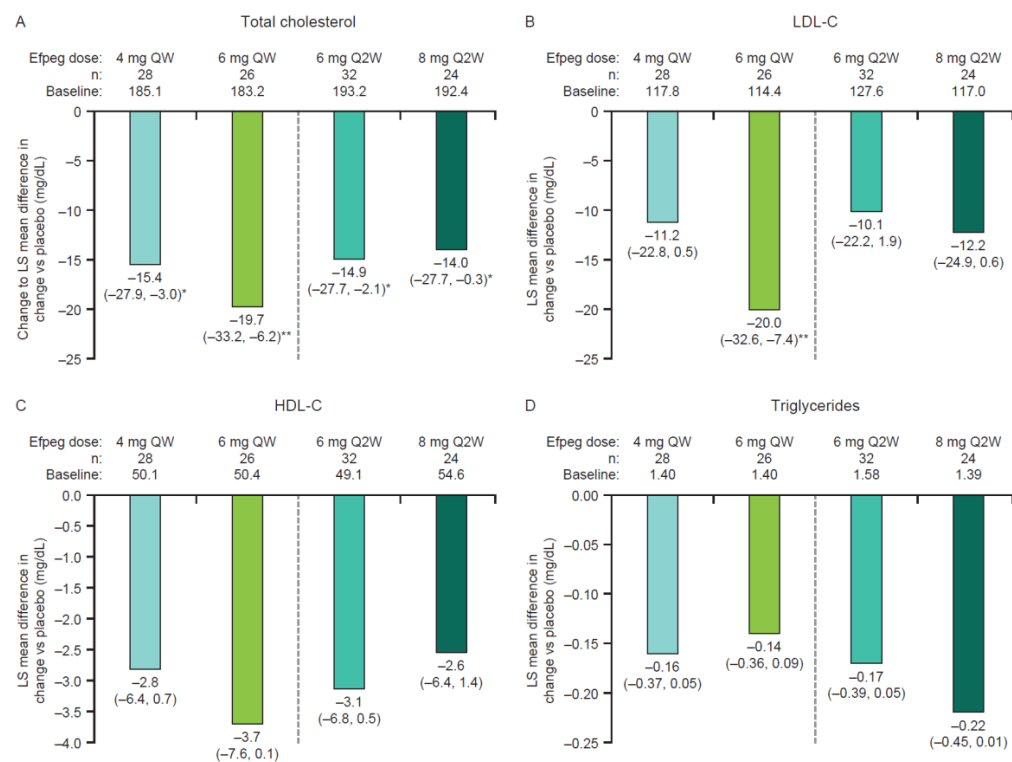
6   95.1% CI data are shown in brackets

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

8   *$p<0.05$; **$p<0.01$

Waist circumference

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10 **Supplementary Figure S3 Patients with prediabetes: change from baseline to Week 21 versus placebo in (a) total cholesterol,**

11 **(b) LDL-C, (c) HDL-C, and (d) triglycerides**

12 95.1% CI data are shown in brackets

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

14 once every 2 weeks

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

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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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20 **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

21 [a]Number of patients who reported at least one event; percentage calculated using subgroup n number as denominator; [b]Gastrointestinal

22 TEAEs included nausea, vomiting, diarrhoea, dyspepsia and constipation; [c]Reported by patients in study diaries (with an alert value of FPG

23 ≤70 mg/dL; no severe cases were reported [defined as hypoglycaemia requiring assistance from another person to administer carbohydrates or

24 glucagon actively, or take other corrective actions])

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

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26 **Supplementary Table S3 Patients stratified by BMI and age at baseline: gastrointestinal treatment-emergent adverse events and**

27 **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%)

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		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%)

7

		Efpeglenatide				Placebo (n=60)
		4mg QW (n=59)	6mg QW (n=59)	6mg Q2W (n=59)	8mg Q2W (n=58)	
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%)

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

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

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