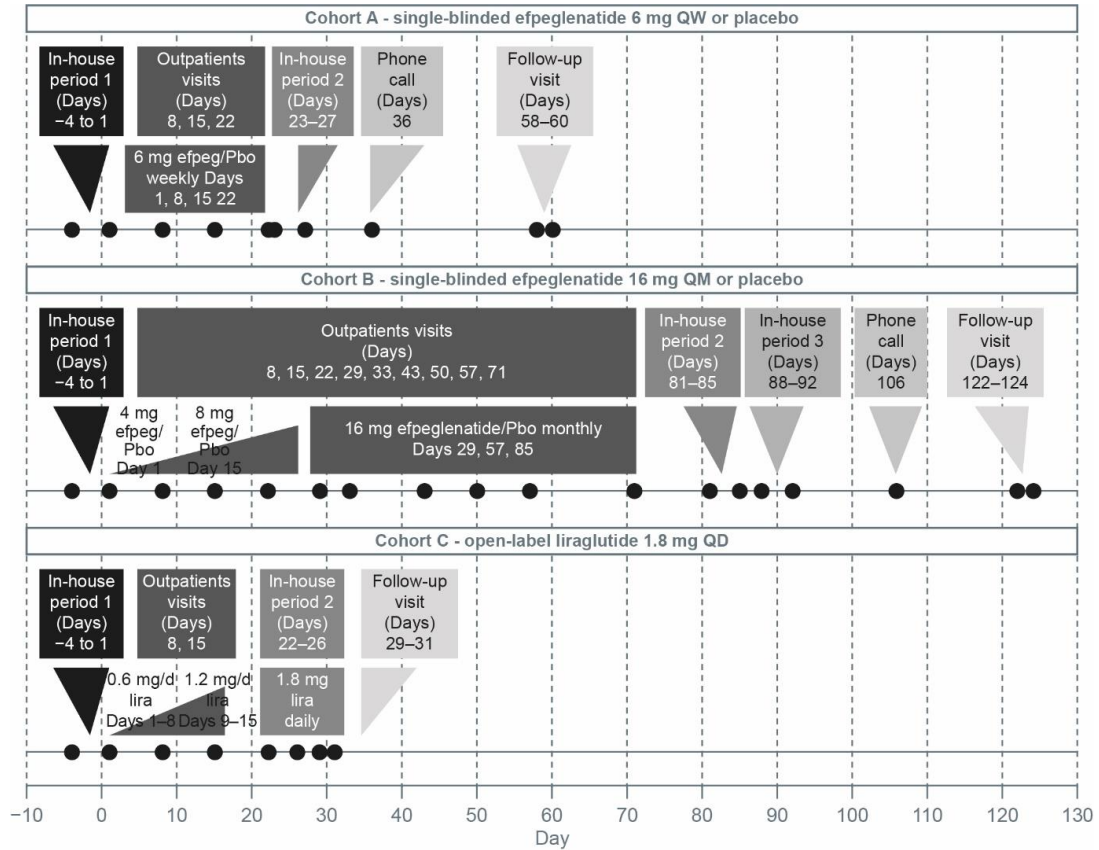


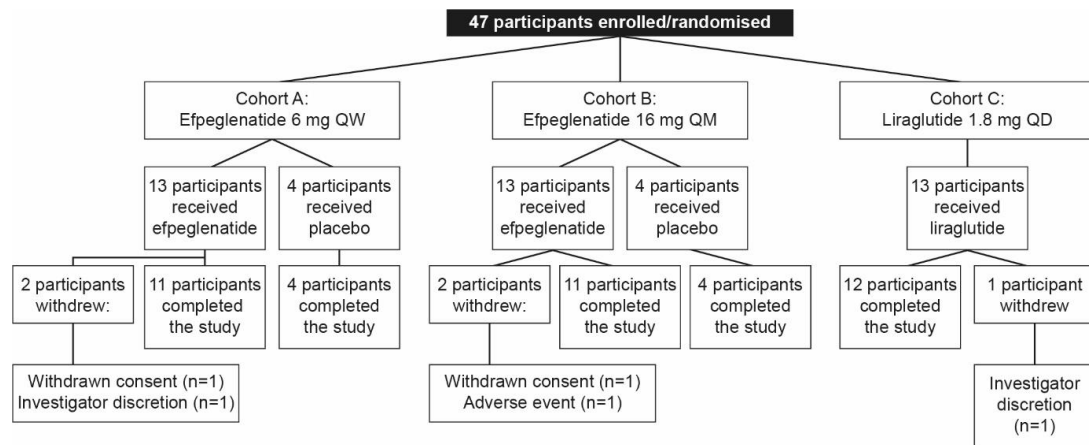
Supplementary Material

Supplementary Figure S1 Study design



Pbo placebo, QD once daily, QM once monthly, QW once weekly.

Supplementary Figure S2 Flow diagram



Supplementary Table S1 PK parameters at peak concentration of efpeglenatide – following a Mixed Meal tolerance test (MMT)

		Comparison	LS mean ratio[‡]	90% CI Lower	90% CI Upper	Nominal P-value[§]
Acetaminophen PK parameters	Efpeglenatide 6 mg QW vs liraglutide	AUC ₀₋₆₀ (h*µg/mL)	1.236	0.703	2.171	0.2652
		AUC ₀₋₁₂₀ (h*µg/mL)	1.275	0.918	1.770	0.1105
		AUC ₀₋₁₈₀ (h*µg/mL)	1.330	0.972	1.820	0.0668
		AUC ₀₋₃₆₀ (h*µg/mL)	1.175	0.839	1.644	0.2122
		C _{max} (µg/mL)	1.206	0.927	1.569	0.1187
	Efpeglenatide 16 mg QM vs liraglutide	AUC ₀₋₆₀ (h*µg/mL)	1.260	0.715	2.221	0.2477
		AUC ₀₋₁₂₀ (h*µg/mL)	1.077	0.781	1.485	0.3495
		AUC ₀₋₁₈₀ (h*µg/mL)	1.031	0.764	1.393	0.4318
		AUC ₀₋₃₆₀ (h*µg/mL)	0.855	0.619	1.181	0.2097
		C _{max} (µg/mL)	0.988	0.769	1.270	0.4690
Efpeglenatide 6 mg QW vs placebo	AUC ₀₋₆₀ (h*µg/mL)	0.459	0.247	0.853	0.0408	
	AUC ₀₋₁₂₀ (h*µg/mL)	0.676	0.473	0.965	0.0713	
	AUC ₀₋₁₈₀ (h*µg/mL)	0.769	0.550	1.076	0.1957	

		AUC ₀₋₃₆₀ (h*µg/mL)	0.899	0.627	1.290	0.6214
		C _{max} (µg/mL)	0.794	0.598	1.054	0.1775
	Efpeglenatide 16 mg QM vs placebo	AUC ₀₋₆₀ (h*µg/mL)	0.468	0.249	0.880	0.0496
		AUC ₀₋₁₂₀ (h*µg/mL)	0.571	0.400	0.816	0.0118
		AUC ₀₋₁₈₀ (h*µg/mL)	0.596	0.426	0.834	0.0133
		AUC ₀₋₃₆₀ (h*µg/mL)	0.655	0.456	0.940	0.0557
		C _{max} (µg/mL)	0.651	0.492	0.860	0.0133
	Liraglutide vs placebo	AUC ₀₋₆₀ (h*µg/mL)	0.372	0.199	0.692	0.0108
		AUC ₀₋₁₂₀ (h*µg/mL)	0.530	0.373	0.754	0.0043
		AUC ₀₋₁₈₀ (h*µg/mL)	0.578	0.416	0.805	0.0081
		AUC ₀₋₃₆₀ (h*µg/mL)	0.765	0.536	1.092	0.2118
		C _{max} (µg/mL)	0.658	0.500	0.866	0.0144
Postprandial plasma glucose	Efpeglenatide 6 mg QW vs liraglutide	AUC ₀₋₆₀ (h*mg/dL)				
			0.938	0.831	1.059	0.1891
		AUC ₀₋₁₂₀ (h*mg/dL)	0.919	0.816	1.035	0.1198
		AUC ₀₋₁₈₀ (h*mg/dL)	0.908	0.811	1.017	0.0799
		AUC ₀₋₃₆₀ (h*mg/dL)	0.891	0.802	0.991	0.0377

		C _{max} (mg/dL)	0.929	0.814	1.059	0.1745
	Efpeglenatide 16 mg QM vs liraglutide	AUC ₀₋₆₀ (h*mg/dL)	0.930	0.820	1.054	0.1679
		AUC ₀₋₁₂₀ (h*mg/dL)	0.928	0.821	1.049	0.1565
		AUC ₀₋₁₈₀ (h*mg/dL)	0.926	0.824	1.039	0.1333
		AUC ₀₋₃₆₀ (h*mg/dL)	0.906	0.813	1.010	0.0663
		C _{max} (mg/dL)	0.922	0.806	1.054	0.1566
	Efpeglenatide 6 mg QW vs placebo	AUC ₀₋₆₀ (h*mg/dL)	0.628	0.548	0.720	<0.0001
		AUC ₀₋₁₂₀ (h*mg/dL)	0.617	0.539	0.706	<0.0001
		AUC ₀₋₁₈₀ (h*mg/dL)	0.607	0.533	0.690	<0.0001
		AUC ₀₋₃₆₀ (h*mg/dL)	0.647	0.573	0.731	<0.0001
		C _{max} (mg/dL)	0.644	0.555	0.747	<0.0001
	Efpeglenatide 16 mg QM vs placebo	AUC ₀₋₆₀ (h*mg/dL)	0.623	0.543	0.715	<0.0001
		AUC ₀₋₁₂₀ (h*mg/dL)	0.623	0.544	0.713	<0.0001
		AUC ₀₋₁₈₀ (h*mg/dL)	0.618	0.543	0.703	<0.0001
		AUC ₀₋₃₆₀ (h*mg/dL)	0.657	0.582	0.743	<0.0001
		C _{max} (mg/dL)	0.639	0.550	0.741	<0.0001
Glucagon	Efpeglenatide 6 mg QW vs liraglutide	AUC ₀₋₆₀ (h*pmol/L)	0.834	0.648	1.074	0.1169

	AUC ₀₋₁₂₀ (h*pmol/L)	0.870	0.661	1.144	0.1980
	AUC ₀₋₁₈₀ (h*pmol/L)	0.878	0.677	1.140	0.2031
	AUC ₀₋₃₆₀ (h*pmol/L)	0.877	0.679	1.132	0.1959
	C _{max} (pmol/L)	0.950	0.716	1.261	0.3804
Efpeglenatide 16 mg QM vs liraglutide	AUC ₀₋₆₀ (h*pmol/L)	0.720	0.561	0.925	0.0165
	AUC ₀₋₁₂₀ (h*pmol/L)	0.700	0.533	0.920	0.0169
	AUC ₀₋₁₈₀ (h*pmol/L)	0.701	0.541	0.908	0.0130
	AUC ₀₋₃₆₀ (h*pmol/L)	0.662	0.514	0.852	0.0044
	C _{max} (pmol/L)	0.747	0.562	0.993	0.0463
Efpeglenatide 6 mg QW vs placebo	AUC ₀₋₆₀ (h*pmol/L)	0.688	0.523	0.903	0.0262
	AUC ₀₋₁₂₀ (h*pmol/L)	0.685	0.509	0.920	0.0371
	AUC ₀₋₁₈₀ (h*pmol/L)	0.680	0.514	0.900	0.0256
	AUC ₀₋₃₆₀ (h*pmol/L)	0.720	0.549	0.945	0.0491
	C _{max} (pmol/L)	0.792	0.581	1.079	0.2119
Efpeglenatide 16 mg QM vs placebo	AUC ₀₋₆₀ (h*pmol/L)	0.594	0.449	0.785	0.0032
	AUC ₀₋₁₂₀ (h*pmol/L)	0.551	0.407	0.747	0.0021
	AUC ₀₋₁₈₀ (h*pmol/L)	0.543	0.407	0.724	0.0010

		AUC ₀₋₃₆₀ (h*pmol/L)	0.544	0.412	0.718	0.0007
		C _{max} (pmol/L)	0.623	0.455	0.854	0.0156
Fasting plasma glucose	Efpeglenatide 6 mg QW vs liraglutide	C _{max} (mg/dL)	0.957	0.840	1.090	0.2865
	Efpeglenatide 16 mg QM vs liraglutide	C _{max} (mg/dL)	0.875	0.765	0.999	0.0490
	Efpeglenatide 6 mg QW vs placebo	C _{max} (mg/dL)	0.699	0.604	0.808	0.0002
	Efpeglenatide 16 mg QM vs placebo	C _{max} (mg/dL)	0.638	0.550	0.741	<0.0001
C-peptide	Efpeglenatide 6 mg QW vs liraglutide	AUC ₀₋₆₀ (h*pmol/L)	1.113	0.941	1.316	0.1439
		AUC ₀₋₁₂₀ (h*pmol/L)	1.227	1.046	1.439	0.0186
		AUC ₀₋₁₈₀ (h*pmol/L)	1.226	1.054	1.425	0.0144
		AUC ₀₋₃₆₀ (h*pmol/L)	1.108	0.960	1.278	0.1175
		C _{max} (pmol/L)	1.315	1.102	1.568	0.0063
	Efpeglenatide 16 mg QM vs liraglutide	AUC ₀₋₆₀ (h*pmol/L)	1.001	0.845	1.185	0.4970
		AUC ₀₋₁₂₀ (h*pmol/L)	1.162	0.987	1.367	0.0644
		AUC ₀₋₁₈₀ (h*pmol/L)	1.210	1.037	1.411	0.0222
		AUC ₀₋₃₆₀ (h*pmol/L)	1.137	0.983	1.316	0.0731
		C _{max} (pmol/L)	1.312	1.096	1.572	0.0077
	Efpeglenatide 6 mg QW vs placebo	AUC ₀₋₆₀ (h*pmol/L)	1.161	0.959	1.405	0.1951

	AUC ₀₋₁₂₀ (h*pmol/L)	1.208	1.004	1.454	0.0927
	AUC ₀₋₁₈₀ (h* pmol/L)	1.181	0.992	1.407	0.1163
	AUC ₀₋₃₆₀ (h*pmol/L)	1.106	0.939	1.303	0.3075
	C _{max} (pmol/L)	1.279	1.040	1.572	0.0520
Efpeglenatide 16 mg QM vs placebo	AUC ₀₋₆₀ (h*pmol/L)	1.044	0.863	1.262	0.7060
	AUC ₀₋₁₂₀ (h*pmol/L)	1.144	0.951	1.375	0.2265
	AUC ₀₋₁₈₀ (h* pmol/L)	1.166	0.980	1.387	0.1453
	AUC ₀₋₃₆₀ (h*pmol/L)	1.135	0.965	1.336	0.1974
	C _{max} (pmol/L)	1.276	1.041	1.565	0.0510

ANOVA analysis of variance, AUC area under the curve, CI confidence interval, C_{max} maximum concentration, LS least squares, PK pharmacokinetic, QM once monthly, QW once weekly.

[†]Calculated using log transformed data.

[‡]Ratio calculated by exponential transformation of mean difference.

[§]From the ANOVA model. One-sided for comparisons versus liraglutide and two-sided for comparisons versus placebo.

Non-inferiority compared to liraglutide was determined based on the lower bound of the 90% CI for the LS mean ratio using a margin of 0.8.

Supplementary Table S2 PK parameters at trough concentration of efpeglenatide 16 mg QW*

	Cohort/ comparison	LS mean [†]	90% CI	90% CI	LS mean	90% CI	90% CI	P-value [§]
			Lower	Upper	ratio [‡]	Lower	Upper	
Acetaminophen PK parameters								
AUC ₀₋₆₀ (h*µg/mL) (24/82/23)	Efpeglenatide 6 mg QW	0.877	0.478	1.276				
	Efpeglenatide 16 mg QM	1.038	0.625	1.451				
	Liraglutide	0.621	0.223	1.020				
	Placebo	1.574	1.090	2.058				
	Efpeglenatide 6 mg QW vs liraglutide				1.292	0.731	2.283	0.2264
	Efpeglenatide 16 mg QM vs liraglutide				1.517	0.856	2.688	0.1135
	Efpeglenatide 6 mg QW vs placebo				0.498	0.267	0.932	0.0683

	Efpeglenatide 16 mg QM vs placebo				0.585	0.310	1.106	0.1642
	Liraglutide vs placebo				0.386	0.206	0.723	0.0147
AUC ₀₋₁₈₀ (h*µg/mL) (24/82/23)	Efpeglenatide 6 mg QW	2.775	2.621	2.929	–	–	–	–
	Efpeglenatide 16 mg QM	2.762	2.608	2.916	–	–	–	–
	Liraglutide	2.493	2.345	2.642	–	–	–	–
	Placebo	3.000	2.822	3.179	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.326	1.064	1.652	0.0187
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.308	1.060	1.615	0.0190
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.799	0.631	1.011	0.1160
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.788	0.623	0.998	0.0966
	Liraglutide vs placebo				0.602	0.478	0.760	0.0007

AUC ₀₋₃₆₀ (h*µg/mL) (24/82/23)	Efpeglenatide 6 mg QW	3.410	3.314	3.506	–	–	–	–
	Efpeglenatide 16 mg QM	3.416	3.319	3.512	–	–	–	–
	Liraglutide	3.273	3.180	3.365	–	–	–	–
	Placebo	3.495	3.384	3.606	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.147	1.001	1.316	0.0492
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.154	1.012	1.316	0.0369
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.919	0.793	1.064	0.3360
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.924	0.797	1.071	0.3716
	Liraglutide vs placebo				0.801	0.693	0.925	0.0134
C _{max} (µg/mL) (24/82/23)	Efpeglenatide 6 mg QW	2.186	2.047	2.324	–	–	–	–
	Efpeglenatide 16 mg QM	2.134	1.996	2.271	–	–	–	–

	Liraglutide	1.937	1.804	2.070	–	–	–	–
	Placebo	2.421	2.261	2.581	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.283	1.052	1.563	0.0204
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.217	1.008	1.470	0.0434
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.790	0.638	0.978	0.0707
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.750	0.608	0.926	0.0266
	Liraglutide vs placebo				0.616	0.501	0.758	0.0003
Postprandial								
Plasma glucose								
AUC _{0–180} (h*mg/dL) (24/82/23)	Efpeglenatide 6 mg QW	6.009	5.922	6.096	–	–	–	–
	Efpeglenatide 16 mg QM	6.336	6.246	6.426	–	–	–	–

	Liraglutide	6.103	6.017	6.190	–	–	–	–
	Placebo	6.530	6.422	6.637	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	0.910	0.805	1.028	0.1001
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.262	1.114	1.431	0.0016
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.594	0.517	0.683	<0.0001
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.824	0.717	0.948	0.0249
AUC _{0–360} (h*mg/dL) (24/82/23)	Efpeglenatide 6 mg QW	6.552	6.469	6.634	–	–	–	–
	Efpeglenatide 16 mg QM	6.821	6.735	6.906	–	–	–	–
	Liraglutide	6.667	6.584	6.749	–	–	–	–
	Placebo	7.012	6.909	7.115	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	0.892	0.794	1.001	0.0519

	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.166	1.036	1.314	0.0177
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.631	0.552	0.721	<0.0001
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.826	0.722	0.944	0.0206
C_{\max} (mg/dL) (24/82/23)	Efpeglenatide 6 mg QW	5.149	5.052	5.246	–	–	–	–
	Efpeglenatide 16 mg QM	5.445	5.344	5.545	–	–	–	–
	Liraglutide	5.215	5.119	5.311	–	–	–	–
	Placebo	5.617	5.499	5.736	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	0.936	0.817	1.073	0.2100
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.258	1.094	1.446	0.0043
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.626	0.537	0.731	<0.0001
	Efpeglenatide 16 mg QM vs	–	–	–	0.842	0.721	0.982	0.0679

placebo								
Insulin								
AUC ₀₋₁₈₀	Efpeglenatide 6 mg QW	5.078	4.894	5.261	–	–	–	–
(h*mU/L)								
(24/82/23)								
	Efpeglenatide 16 mg QM	5.077	4.887	5.267	–	–	–	–
	Liraglutide	4.656	4.474	4.838	–	–	–	–
	Placebo	4.886	4.662	5.111	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.524	1.176	1.976	0.0046
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.524	1.171	1.983	0.0052
	Efpeglenatide 6 mg QW vs placebo	–	–	–	1.211	0.904	1.622	0.2766
	Efpeglenatide 16 mg QM vs placebo	–	–	–	1.210	0.902	1.624	0.2799
AUC ₀₋₃₆₀	Efpeglenatide 6 mg QW	5.392	5.219	5.565	–	–	–	–

(h*mU/L)								
(24/82/23)								
	Efpeglenatide 16 mg QM	5.472	5.294	5.650	–	–	–	–
	Liraglutide	5.136	4.966	5.307	–	–	–	–
	Placebo	5.265	5.057	5.474	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.292	1.012	1.649	0.0428
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.399	1.094	1.789	0.0134
	Efpeglenatide 6 mg QW vs placebo	–	–	–	1.135	0.865	1.491	0.4369
	Efpeglenatide 16 mg QM vs placebo	–	–	–	1.230	0.936	1.617	0.2100
C _{max} (mU/L)	Efpeglenatide 6 mg QW	4.505	4.283	4.728	–	–	–	–
(24/82/23)								
	Efpeglenatide 16 mg QM	4.416	4.185	4.647	–	–	–	–
	Liraglutide	3.933	3.712	4.154	–	–	–	–

	Placebo	4.149	3.876	4.421	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.773	1.296	2.427	0.0019
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.621	1.178	2.232	0.0075
	Efpeglenatide 6 mg QW vs placebo	–	–	–	1.429	1.002	2.036	0.0980
	Efpeglenatide 16 mg QM vs placebo	–	–	–	1.306	0.914	1.866	0.2142
Glucagon								
AUC _{0–180} (h*pmol/L) (24/82/23)	Efpeglenatide 6 mg QW	3.457	3.291	3.622	–	–	–	–
	Efpeglenatide 16 mg QM	3.642	3.472	3.813	–	–	–	–
	Liraglutide	3.581	3.413	3.749	–	–	–	–
	Placebo	3.867	3.665	4.070	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	0.883	0.694	1.123	0.1941

	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.063	0.837	1.350	0.3336
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.663	0.512	0.859	0.0109
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.799	0.612	1.042	0.1620
AUC _{0–360} (h*pmol/L) (24/82/23)	Efpeglenatide 6 mg QW	4.255	4.084	4.426	–	–	–	–
	Efpeglenatide 16 mg QM	4.421	4.246	4.596	–	–	–	–
	Liraglutide	4.377	4.204	4.550	–	–	–	–
	Placebo	4.594	4.388	4.800	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	0.885	0.690	1.135	0.2074
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.045	0.818	1.336	0.3818
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.713	0.547	0.929	0.0375

	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.841	0.641	1.103	0.2880
C_{\max} (pmol/L) (24/82/23)	Efpeglenatide 6 mg QW	2.859	2.684	3.034	–	–	–	–
	Efpeglenatide 16 mg QM	2.980	2.799	3.161	–	–	–	–
	Liraglutide	2.918	2.741	3.094	–	–	–	–
	Placebo	3.122	2.909	3.334	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	0.943	0.734	1.213	0.3486
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.064	0.827	1.370	0.3398
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.769	0.584	1.012	0.1151
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.868	0.656	1.147	0.3973
Fasting plasma glucose								
C_{\max} (mg/dL)	Efpeglenatide 6 mg QW	4.746	4.652	4.841	–	–	–	–

(24/82/23)								
	Efpeglenatide 16 mg QM	4.856	4.757	4.954	–	–	–	–
	Liraglutide	4.788	4.692	4.883	–	–	–	–
	Placebo	5.117	5.000	5.234	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	0.959	0.839	1.097	0.3031
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.070	0.933	1.228	0.2050
	Efpeglenatide 6 mg QW vs placebo	–	–	–	0.690	0.594	0.802	0.0002
	Efpeglenatide 16 mg QM vs placebo	–	–	–	0.770	0.661	0.897	0.0065
C-peptide								
AUC _{0–180} (h*pmol/L)	Efpeglenatide 6 mg QW	8.751	8.640	8.862	–	–	–	–
(24/82/23)								
	Efpeglenatide 16 mg QM	8.746	8.631	8.861	–	–	–	–

	Liraglutide	8.545	8.434	8.655	–	–	–	–
	Placebo	8.628	8.490	8.767	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.229	1.052	1.437	0.0158
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.223	1.043	1.434	0.0197
	Efpeglenatide 6 mg QW vs placebo	–	–	–	1.131	0.944	1.355	0.2581
	Efpeglenatide 16 mg QM vs placebo	–	–	–	1.125	0.940	1.347	0.2752
AUC _{0–360} (h*pmol/L) (24/82/23)	Efpeglenatide 6 mg QW	9.253	9.155	9.352	–	–	–	–
	Efpeglenatide 16 mg QM	9.318	9.217	9.420	–	–	–	–
	Liraglutide	9.153	9.055	9.250	–	–	–	–
	Placebo	9.216	9.095	9.336	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.106	0.964	1.270	0.1126

	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.180	1.025	1.359	0.0272
	Efpeglenatide 6 mg QW vs placebo	–	–	–	1.038	0.887	1.216	0.6890
	Efpeglenatide 16 mg QM vs placebo	–	–	–	1.108	0.947	1.296	0.2765
C_{\max} (pmol/L) (24/82/23)	Efpeglenatide 6 mg QW	7.965	7.837	8.094	–	–	–	–
	Efpeglenatide 16 mg QM	7.938	7.805	8.071	–	–	–	–
	Liraglutide	7.690	7.562	7.817	–	–	–	–
	Placebo	7.771	7.609	7.932	–	–	–	–
	Efpeglenatide 6 mg QW vs liraglutide	–	–	–	1.317	1.100	1.577	0.0069
	Efpeglenatide 16 mg QM vs liraglutide	–	–	–	1.282	1.066	1.541	0.0144
	Efpeglenatide 6 mg QW vs placebo	–	–	–	1.215	0.984	1.500	0.1281
	Efpeglenatide 16 mg QM vs	–	–	–	1.182	0.960	1.456	0.1835

placebo

AUC area under the curve, *CI* confidence interval, *LS* least squares, *PK* pharmacokinetic, *QD* once daily, *QM* once monthly, *QW* once weekly.

[^]Trough concentration of efpeglenatide 16 mg QM was assessed on day 82. Please note that the concentrations above for efpeglenatide 6 mg QW and liraglutide 1.8 mg QD were assessed on days 24 and 23, respectively, when they were at peak or steady-state concentrations.

[†]Calculated using log-transformed data.

[‡]Ratio calculated by exponential transformation of mean difference.

[§]From the ANOVA model. One-sided for comparisons versus liraglutide and two-sided for comparisons versus placebo.

Noninferiority compared to liraglutide was determined based on the lower bound of the 90% CI for the LS mean ratio using a margin of 0.8.

Significance was determined based on a two-tailed *p*-value less than 0.05.

Supplementary Table S3 Plasma insulin concentration parameters at peak concentration of efpeglenatide

		Comparison	LS mean ratio[‡]	90% CI Lower	90% CI Upper	Nominal P-value[§]
Insulin	Efpeglenatide 6 mg QW vs liraglutide	AUC ₀₋₆₀ (h*mU/L)	1.236	0.950	1.606	0.0910
		AUC ₀₋₁₂₀ (h*mU/L)	1.532	1.190	1.973	0.0035
		AUC ₀₋₁₈₀ (h*mU/L)	1.516	1.208	1.902	0.0019
		AUC ₀₋₃₆₀ (h*mU/L)	1.298	1.037	1.625	0.0290
		C _{max} (mU/L)	1.765	1.331	2.342	0.0008
	Efpeglenatide 16 mg QM vs liraglutide	AUC ₀₋₆₀ (h*mU/L)	1.012	0.776	1.319	0.4697
		AUC ₀₋₁₂₀ (h*mU/L)	1.264	0.978	1.635	0.0661
		AUC ₀₋₁₈₀ (h*mU/L)	1.330	1.056	1.675	0.0218
		AUC ₀₋₃₆₀ (h*mU/L)	1.203	0.960	1.509	0.0878
		C _{max} (mU/L)	1.440	1.080	1.920	0.0196
	Efpeglenatide 6 mg QW vs placebo	AUC ₀₋₆₀ (h*mU/L)	1.192	0.889	1.598	0.3190
		AUC ₀₋₁₂₀ (h*mU/L)	1.356	1.020	1.803	0.0797
		AUC ₀₋₁₈₀ (h*mU/L)	1.309	1.014	1.691	0.0840
		AUC ₀₋₃₆₀ (h*mU/L)	1.223	0.952	1.572	0.1830

	C_{\max} (mU/L)	1.539	1.118	2.118	0.0285
Efpeglenatide 16 mg QM vs placebo	AUC_{0-60} (h*mU/L)	0.976	0.727	1.312	0.8921
	AUC_{0-120} (h*mU/L)	1.119	0.839	1.492	0.5137
	AUC_{0-180} (h*mU/L)	1.149	0.888	1.486	0.3689
	AUC_{0-360} (h*mU/L)	1.134	0.882	1.459	0.4038
	C_{\max} (mU/L)	1.256	0.911	1.731	0.2396

[‡]Ratio calculated by exponential transformation of mean difference.

[§]From the ANOVA model. One-sided for comparisons versus liraglutide and two-sided for comparisons versus placebo.

Plasma insulin concentrations (Figure 2E) were not significantly different between placebo and efpeglenatide 6 mg QW or 16 mg QM, with the exception of C_{\max} for efpeglenatide 6 mg versus placebo ($p=0.0285$). AUC_{0-180} , AUC_{0-360} , and C_{\max} were significantly greater with both efpeglenatide groups versus liraglutide ($p<0.05$ for all).

Supplementary Table S4 Number (%) of patients with adverse events related to study drug, according to severity (n>1 in any group) (safety population)

	Cohort A						Cohort B						Cohort C		
	Efpeglenatide 6 mg QW			Placebo			Efpeglenatide 16 mg QM			Placebo			Liraglutide		
	Mild	Moderate	Total	Mild	Moderate	Total	Mild	Moderate	Total	Mild	Moderate	Total	Mild	Moderate	Total
Gastrointestinal disorders, n (%)															
Diarrhoea	5 (38.5)	–	5 (38.5)	1 (25.0)	–	1 (25.0)	7 (53.8)	–	7 (53.8)	–	–	–	2 (15.4)	–	2 (15.4)
Nausea	5 (38.5)	–	5 (38.5)	–	–	–	7 (53.8)	1 (7.7)	8 (61.5)	1 (25.0)	–	1 (25.0)	4 (30.8)	–	4 (30.8)
Vomiting	3 (23.1)	–	3 (23.1)	–	–	–	4 (30.8)	2 (15.4)	6 (46.2)	–	–	–	1 (7.7)	1 (7.7)	2 (15.4)
Flatulence	1 (7.7)	–	1 (7.7)	–	–	–	4 (30.8)	–	4 (30.8)	–	–	–	–	–	–
Abdominal distension	1 (7.7)	–	1 (7.7)	–	–	–	3 (23.1)	–	3 (23.1)	–	–	–	2 (15.4)	–	2 (15.4)
Abdominal pain	–	–	–	–	–	–	2 (15.4)	–	2 (15.4)	–	–	–	–	–	–
Eructation	–	–	–	–	–	–	1 (7.7)	–	1 (7.7)	–	–	–	2 (15.4)	–	2 (15.4)
General disorders and administration site conditions, n (%)															
Injection-site pain	2 (15.4)	–	2 (15.4)	–	–	–	1 (7.7)	–	1 (7.7)	1 (25.0)	–	1 (25.0)	–	–	–
Early satiety	1 (7.7)	–	1 (7.7)	–	–	–	3 (23.1)	–	3 (23.1)	–	–	–	–	–	–
Metabolism and nutrition disorders, n (%)															
Decreased appetite	4 (30.8)	–	4 (30.8)	–	–	–	4 (30.8)	–	4 (30.8)	–	–	–	2 (15.4)	–	2 (15.4)
Hypoglycaemia	7 (53.8)	–	7 (53.8)	–	–	–	4 (30.8)	1 (7.7)	5 (38.5)	–	–	–	1 (7.7)	–	1 (7.7)

QM once monthly, QW once weekly.