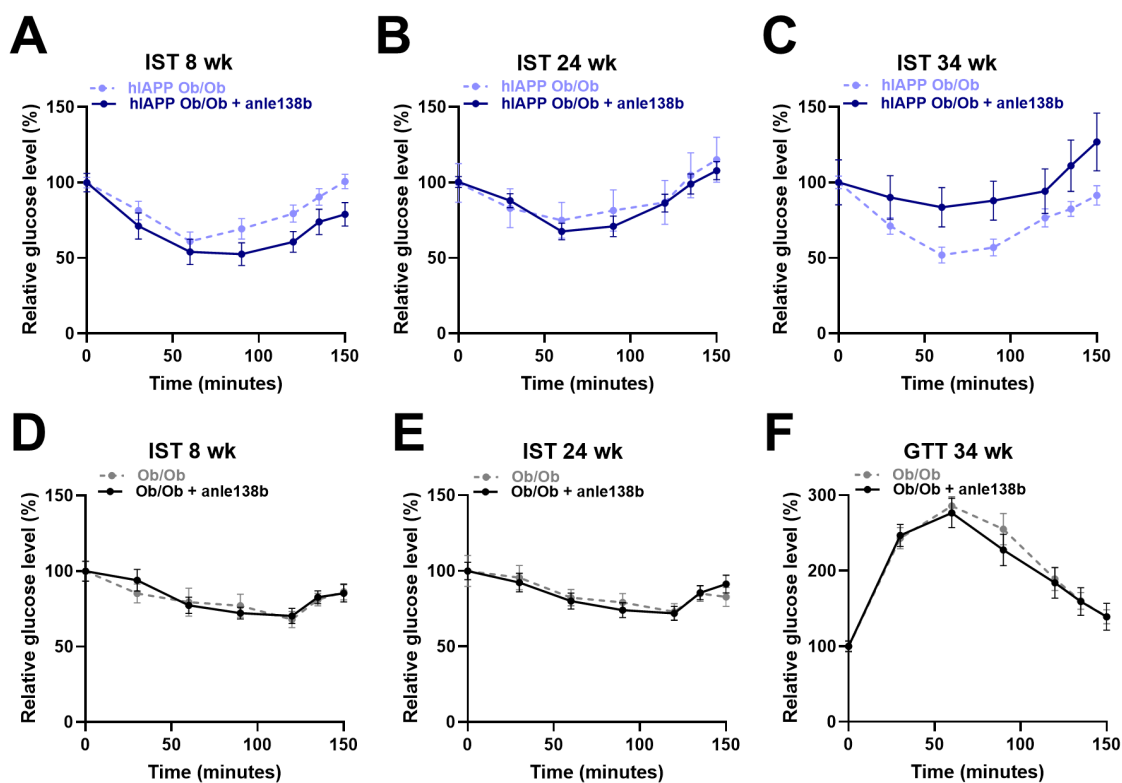
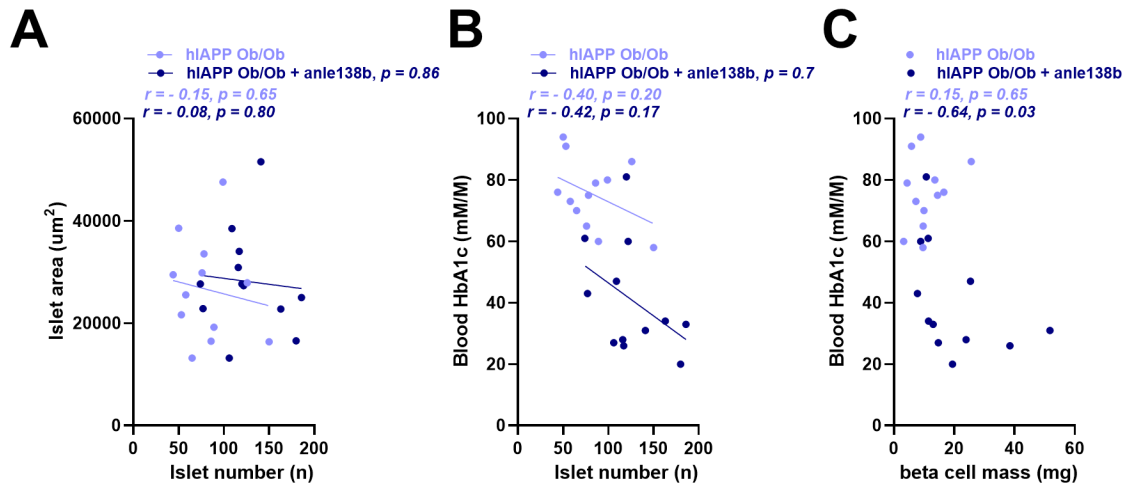


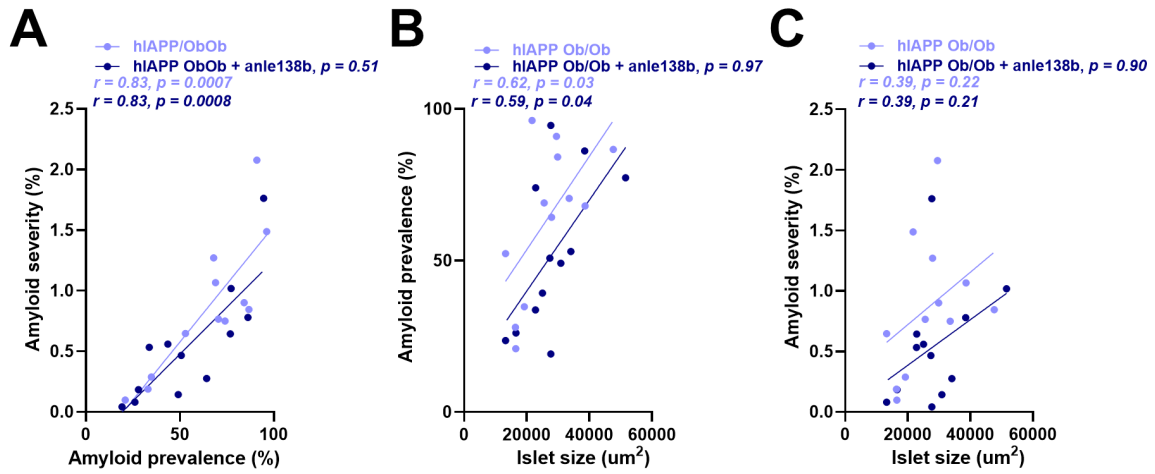
Suppl. Figure 1. Plasma IAPP levels, bodyweight and food intake of Ob/Ob and hIAPP Ob/Ob mice, with and without anle138b treatment. (A) Basal plasma IAPP levels of Ob/Ob and hIAPP Ob/Ob mice determined after 4 h fasting in the morning (t=0 weeks), after 6 h fasting in the morning (at 23 weeks) or after overnight fasting (at 16 and 32 weeks) (n= 12-15 per group at each timepoint), (B) Bodyweight of Ob/Ob and hIAPP Ob/Ob mice determined after 4 h fasting in the morning (t=0 weeks), after 6 h fasting in the morning (at 8, 23, 24 and 34 weeks) or after overnight fasting (at 16 and 32 weeks) (n= 12-15 per group at each time point), (C) Daily food intake determined at 24-27 weeks of treatment for Ob/Ob mice (n= 9-10) and at 28-33 weeks of treatment for hIAPP Ob/Ob mice (n=12). Two-way ANOVA with Tukey's test; for anle138b-treated vs untreated mice.



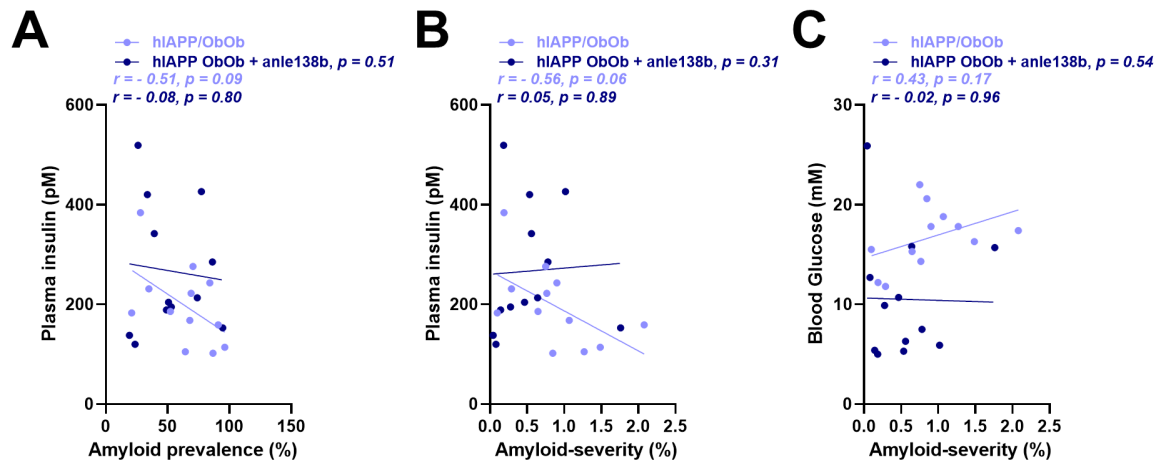
Suppl. Figure 2. Insulin sensitivity in hIAPP Ob/Ob and Ob/Ob mice, with and without anle138b treatment. (A-C) Insulin sensitivity test (IST) of hIAPP Ob/Ob mice after 8, 24 and 34 weeks of treatment, respectively, (D, E) IST of Ob/Ob mice after 8 and 24 weeks of treatment, respectively, and (F) glucose tolerance test (GTT) of Ob/Ob mice after 34 weeks of treatment (n= 12-18 per group at each time point). Insulin sensitivity and glucose tolerance were assessed by intraperitoneal injection of insulin (3 units/kg in Ob/Ob mice at 8 weeks, 4 units/kg in Ob/Ob mice at 24 weeks and 2.25 units/kg in hIAPP Ob/Ob mice at 8, 24 and 34 weeks) or glucose (0.8 gr/kg), respectively, after 6 h of fasting from 7 am onwards. Direct blood glucose measurements were performed immediately before injection and over a period of 150 min after injection. Blood glucose levels are indicated relative to the level at t=0 min. Data are presented as mean \pm SEM; Two-way ANOVA with Sidak's test; for anle138b-treated vs untreated mice.



Suppl. Figure 3. Histomorphology of pancreatic islets from hiAPP Ob/Ob mice, with and without anle138b treatment. (A) Correlation between pancreatic islet number and islet size (average cross-sectional islet area), determined from 3 pancreatic sections per mouse. (B, C) Correlations between (B) islet number and (C) pancreatic beta cell mass (both determined after 36 weeks) and blood HbA1c levels (determined after 32 weeks). All experiments were performed in male mice (n=12 per group). (A, B) Pearson Correlation test and (C) Spearman Correlation test (because of non-normality of the data); correlation coefficient (r) and two-tailed p-value are indicated for both the treated and the untreated mice. (A, B) Linear regression was performed to examine if the slopes of the two regression lines are significantly different (p-value indicated at the top of the figures).



Suppl. Figure 4. Correlations between pancreatic islet amyloid content and islet size of hIAPP Ob/Ob mice, with and without anle138b treatment. (A) Correlation between amyloid prevalence and amyloid severity. (B, C) Correlations between islet size and amyloid prevalence and between islet size and amyloid severity, respectively. All experiments were performed in male mice ($n=12$ per group). Pearson Correlation test; correlation coefficient (r) and two-tailed p -value are indicated for both the treated and the untreated mice. Linear regression was performed to examine if the slopes of the two regression lines are significantly different (p -value indicated at the top of the figures).



Suppl. Figure 5. Correlations between pancreatic islet amyloid content and metabolic parameters of hiAPP Ob/Ob mice, with and without anle138b treatment. (A) Correlations between amyloid prevalence and plasma insulin levels. (B, C) Correlations between amyloid severity and plasma insulin levels and blood glucose levels, respectively. All experiments were performed in male mice ($n=12$ per group). Pearson Correlation test; correlation coefficient (r) and two-tailed p -value are indicated for both the treated and the untreated mice. Linear regression was performed to examine if the slopes of the two regression lines are significantly different (p -value indicated at the top of the figures).