Supplemental Table 1: Covariate analysis of short- and long-term metreleptin therapy

	Period 1 versus Period 2		Period 1 versus 6 month follow-up	Period 2 versus 6 month follow-up
Variable	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin withdrawal cohort**	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin Initiation Cohort**
Peripheral Insulin Sensitivity (M) ($mg/kg_{FFM}/min$)	Period (0.001) Race (0.12)	Period (0.01) Age (0.19)	Period (0.006) Race (0.04)	Period (0.048) Age (0.20) Sex (0.01) Race (0.94) Leptin (0.05)
Hepatic Insulin Sensitivity (% Suppression of Hepatic Glucose Production)	Period (0.008) Sex (0.04) LD Type (0.01) Leptin (0.12)	Period (0.65) Mean EI (0.07)	Period (0.02)	Period (0.37) Sex (0.05)
Fasting Plasma Glucose (mg/dL)	Period (0.003) Age (0.009) LD Type (0.01) Leptin (0.06) Baseline (0.12)	Period (0.49) Race (0.15) Leptin (0.17)	Period (0.03) Baseline (0.08)	Period (0.51) Age (0.15) Baseline (0.02)
24-hour urine glucose excretion[1] (g/24hr)	Period (0.87)	Period (0.24) Age (0.13)	Period (0.03) LD Type (0.16)	Period (0.14)
Hemoglobin A1c[1] (%)	Period[2] (0.003) Mean EI (0.24) LD Type (0.02)	Period (0.13)	Period (0.01)	Period (0.04)
C-peptide (μU/mL)	Period (0.53) Age (0.20) Mean EI (0.32) Baseline (0.002)	Period (0.08) Baseline (0.09)	Period (0.38) Baseline (0.004)	Period (0.19) Baseline (0.0009)
Triglycerides (mg/dL)	Period (0.01) Baseline (<0.0001)	Period (0.21) Baseline (0.43)	Period (0.18)	Period (0.50) LD Type (0.13) Baseline (0.02)
Total Cholesterol (mg/dL)	Period (0.02) Baseline (0.0006)	Period (0.28) Age (0.07) Baseline (0.0001)	Period (0.046) Baseline (<0.0001)	Period (0.97) Race (0.13)
HDL-C (mg/dL)	Period (0.22) Age (0.28) Mean EI (0.74) Leptin (0.05)	Period (0.07) Leptin (0.02)	Period (0.68) Sex (0.12) Leptin (0.02)	Period (0.06) Leptin (0.002)
LDL-C (mg/dL)	Period (0.21) Baseline (0.002)	Period (0.08) Baseline (0.02)	Period (0.05) Baseline (0.01)	Period (0.06) Baseline (0.001)
FFA (mg/dL)	Period (0.72) Age (0.08) Sex (0.22) LD Type (0.04) Leptin (0.10)	Period (0.43) Mean EI (0.03) Sex (0.07)	Period (0.60)	Period (0.62) Leptin (0.16)
Glycerol turnover ($mg/kgL_{BM}/min$)	Period (0.25)	Period (0.89)	Period (0.04)	Period (0.009) Age (0.007) LD Type (0.02) Leptin (0.10)

Palmitate turnover ($mg/kg_{LBM}/min$)	Period (0.14) Age (0.0001) Sex (<0.0001) Race (0.004) LD Type (<0.0001)	Period (0.44) Sex (0.13)	Period (0.02) Sex (0.14)	Period (0.06) Age (0.01) Sex (0.006) Race (0.12) LD Type (0.01)
Hepatic triglyceride content (%)	Period (0.04) Mean EI (0.82) Race (0.25) LD Type (0.45) Leptin (0.41)	Period (0.78) Mean EI (0.15) Race (0.18) Leptin (0.009)	Period (0.007) Sex (0.11)	Period (0.12) Sex (0.15)
ALT (U/L)	Period (0.02) Age (0.03) Sex (0.11) LD Type (0.009) Leptin (0.14) Baseline (0.01)	Period ([3]) Race ([3]) Baseline ([3])	Period (0.04)	Period (0.01) Baseline (0.02)
AST (U/L)	Period (0.04) Baseline (0.03)	Period (0.41) Race (0.16)	Period (0.049)	Period (0.22) Baseline (0.03)

For each outcome of interest, variables included in the final model and p-value (in parentheses) are shown. Period was included in all final models to assess the effect of metreleptin. Additional potential covariates included in each model were: Baseline (baseline value of the outcome prior to study diet), Age, Sex, Race, Mean EI (mean energy intake), Leptin (endogenous leptin level prior to metreleptin treatment), and lipodystrophy type (generalized versus partial, in the initiation cohort only as all subjects in the withdrawal cohort had generalized lipodystrophy).

[1]Baseline value was not included as a covariate for hemoglobin A1c and 24-hour urine glucose excretion due to lack of baseline values.

[2]Change in hemoglobin A1c was not independent of food intake, as it was affected by mean glucose for 3 months prior to study entry and controlled diet.

[3]Unable to determine p-value due to small sample size.

Supplemental Table 2: Effects of ectopic lipid on insulin sensitivity during short- and long-term metreleptin therapy

	Period 1 versus Period 2		Period 1 versus 6 month follow-up	Period 2 versus 6 month follow-up
Variable	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin withdrawal cohort**	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin Initiation Cohort**
Peripheral Insulin Sensitivity (M) ($mg/kg_{FFM}/min$)	Period (0.049) Liver fat (0.025) Lvast IMCL (0.39) Tibant IMCL (0.064)	Period (0.014)	Period (0.089) Liver fat (0.012) Lvast IMCL (0.072)	Period (0.32) Liver fat (0.018) Lvast IMCL (0.039)
Hepatic Insulin Sensitivity (% Suppression of Hepatic Glucose Production)	Period (0.094) Sex (0.04) Age (0.013) Liver fat (0.005) Lvast IMCL (0.053) Tibant IMCL (0.22)	Period (0.95) Age (0.64) Sex (0.91) Liver fat (0.19) Lvast IMCL (0.20)	Period (0.053) Liver fat (0.061)	Period (0.62) Age (0.13) Liver fat (0.028)

For each outcome of interest, variables included in the final model and p-value (in parentheses) are shown. Period was included in all final models to assess the effect of metreleptin. Additional potential covariates included in each model were: Age, Sex, Hepatic triglyceride content (Liver fat), and Intramyocellular lipid content in the vastus lateralis muscle (Lvast IMCL), the tibialis anterior muscle (Tibant IMCL), and the soleus muscle.

Supplemental Table 3: Effects of hepatic triglyceride on insulin sensitivity during short- and long-term metreleptin therapy

	Period 1 versus Period 2		Period 1 versus 6 month follow-up	Period 2 versus 6 month follow-up
Variable	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin withdrawal cohort**	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin Initiation Cohort**
Peripheral Insulin Sensitivity (M) ($mg/kg_{FFM}/min$)	Period (0.031) Liver fat (0.019)	Period (0.014)	Period (0.089) Liver fat (0.012)	Period (0.17) Sex (0.051) Liver fat (0.094)
Hepatic Insulin Sensitivity (% Suppression of Hepatic Glucose Production)	Period (0.058) Sex (0.18) Age (0.074) Liver fat (0.10)	Period (0.53)	Period (0.053) Liver fat (0.061)	Period (0.62) Age (0.13) Liver fat (0.028)

For each outcome of interest, variables included in the final model and p-value (in parentheses) are shown. Period was included in all final models to assess the effect of metreleptin. Additional potential covariates included in each model were: Age, Sex, and Hepatic triglyceride content (Liver fat).

Supplemental Table 4: Effects of intramyocellular triglyceride on insulin sensitivity during short- and long-term metreleptin therapy

	Period 1 versus Period 2		Period 1 versus 6 month follow-up	Period 2 versus 6 month follow-up
Variable	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin withdrawal cohort**	**Final Model: Metreleptin Initiation Cohort**	**Final Model: Metreleptin Initiation Cohort**
Peripheral Insulin Sensitivity (M) ($mg/kg_{FFM}/min$)	Period (0.0015) Sex (0.030) Tibant IMCL (0.0055)	Period (0.014)	Period (0.0061) Sex (0.041)	Period (0.066) Sex (0.0078)
Hepatic Insulin Sensitivity (% Suppression of Hepatic Glucose Production)	Period (0.0026) Sex (0.022) Age (0.22) Tibant IMCL (0.095)	Period (0.40) Lvast IMCL (0.49)	Period (0.017)	Period (0.37) Sex (0.052)

For each outcome of interest, variables included in the final model and p-value (in parentheses) are shown. Period was included in all final models to assess the effect of metreleptin. Additional potential covariates included in each model were: Age, Sex, and Intramyocellular lipid content in the vastus lateralis muscle (Lvast IMCL), the tibialis anterior muscle (Tibant IMCL), and the soleus muscle.