**Figure S1.** (Top) Body weight changes during placebo and Dexfenfluramine treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect of Dexfenfluramine on energy intake along with the exponential best-fit curve.

**Figure S2.** (Top) Body weight changes during placebo and Diethylpropion treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect of Diethylpropion on energy intake along with the exponential best-fit curve.

**Figure S3.** (Top) Body weight changes during placebo and Exenatide treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect of Exenatide on energy intake along with the exponential best-fit curve.

**Figure S4.** (Top) Body weight changes during placebo and Fenproporex treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect of Fenproporex on energy intake along with the exponential best-fit curve.

**Figure S5.** (Top) Body weight changes during placebo and Fluoxetine treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect of Fluoxetine on energy intake along with the exponential best-fit curve.

**Figure S6.** (Top) Body weight changes during placebo and Liraglutide treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect of Liraglutide on energy intake along with the exponential best-fit curve.

**Figure S7.** (Top) Body weight changes during placebo and Mazindol treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect of Mazindol on energy intake along with the exponential best-fit curve.

**Figure S8.** (Top) Body weight changes during placebo and Naltrexone/Bupropion treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S9.** (Top) Body weight changes during placebo and Orlistat treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S10.** (Top) Body weight changes during placebo and Orlistat treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along

with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S11.** (Top) Body weight changes during placebo and Phentermine/Fenfluramine treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S12.** (Top) Body weight changes during placebo and Phentermine/Topiramate treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S13.** (Top) Body weight changes during placebo and Phentermine/Topiramate treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S14.** (Top) Body weight changes during placebo and Phentermine/Topiramate treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S15.** (Top) Body weight changes during placebo and Rimonabant treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S16.** (Top) Body weight changes during placebo and Sibutramine treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S17.** (Top) Body weight changes during placebo and Sibutramine treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

**Figure S18.** (Top) Body weight changes during placebo and Sibutramine treatment. (Mid) Model-calculated changes in energy intake corresponding to the measured body weight trajectories along with the exponential best-fit curves. (Bottom) Model-calculated placebo-subtracted effect on energy intake along with the exponential best-fit curve.

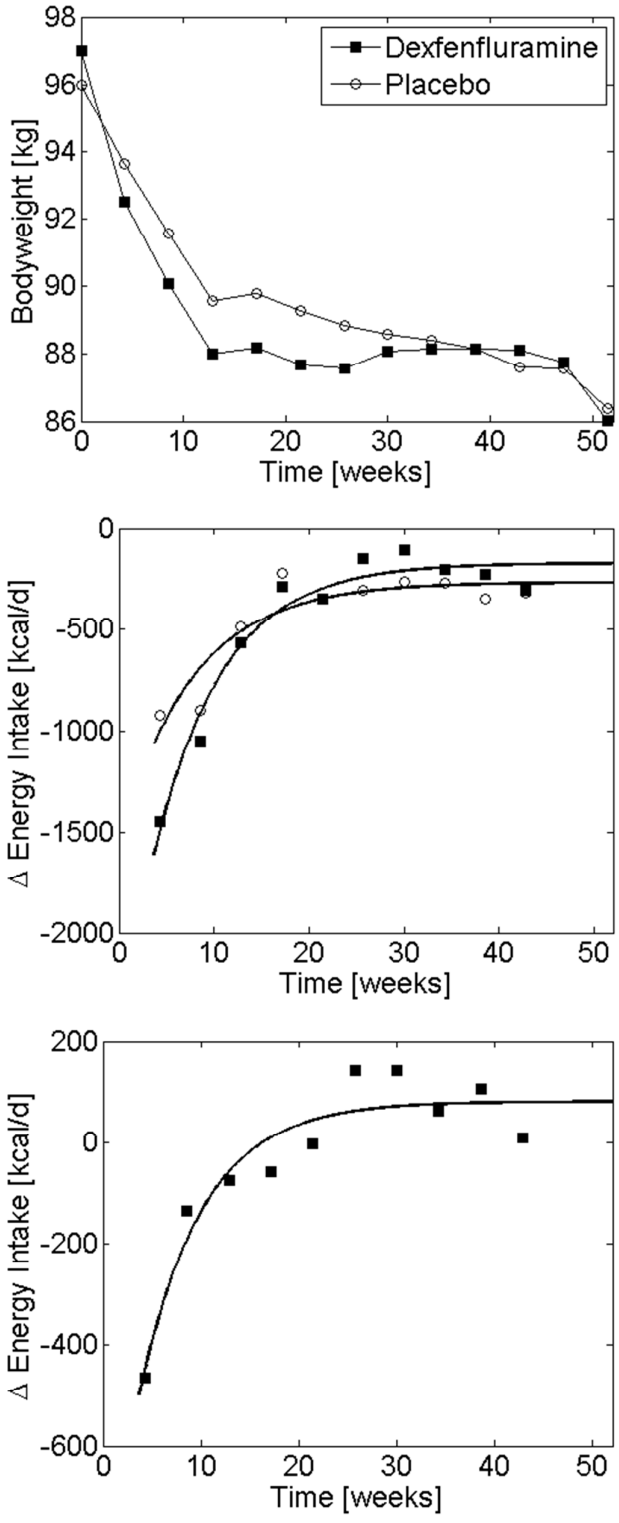

Dexfenfluramine
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S1.**

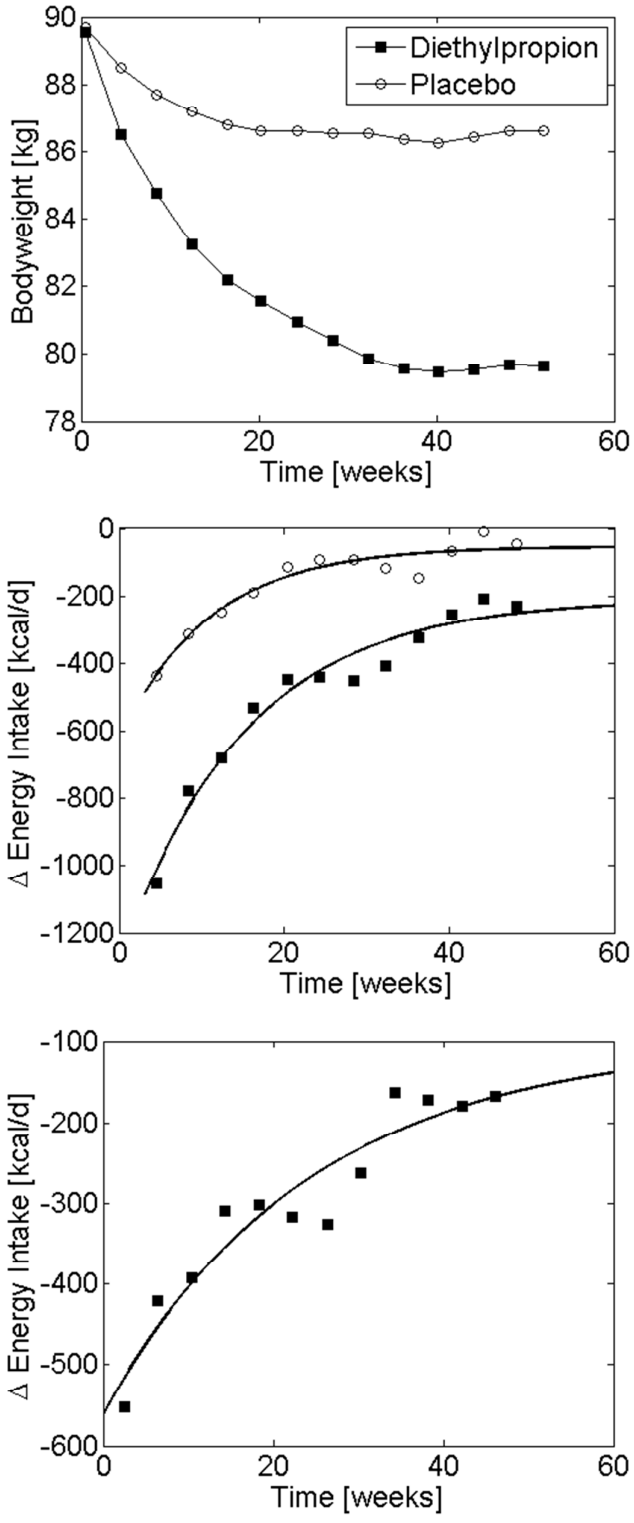

Diethylpropion
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S2.**

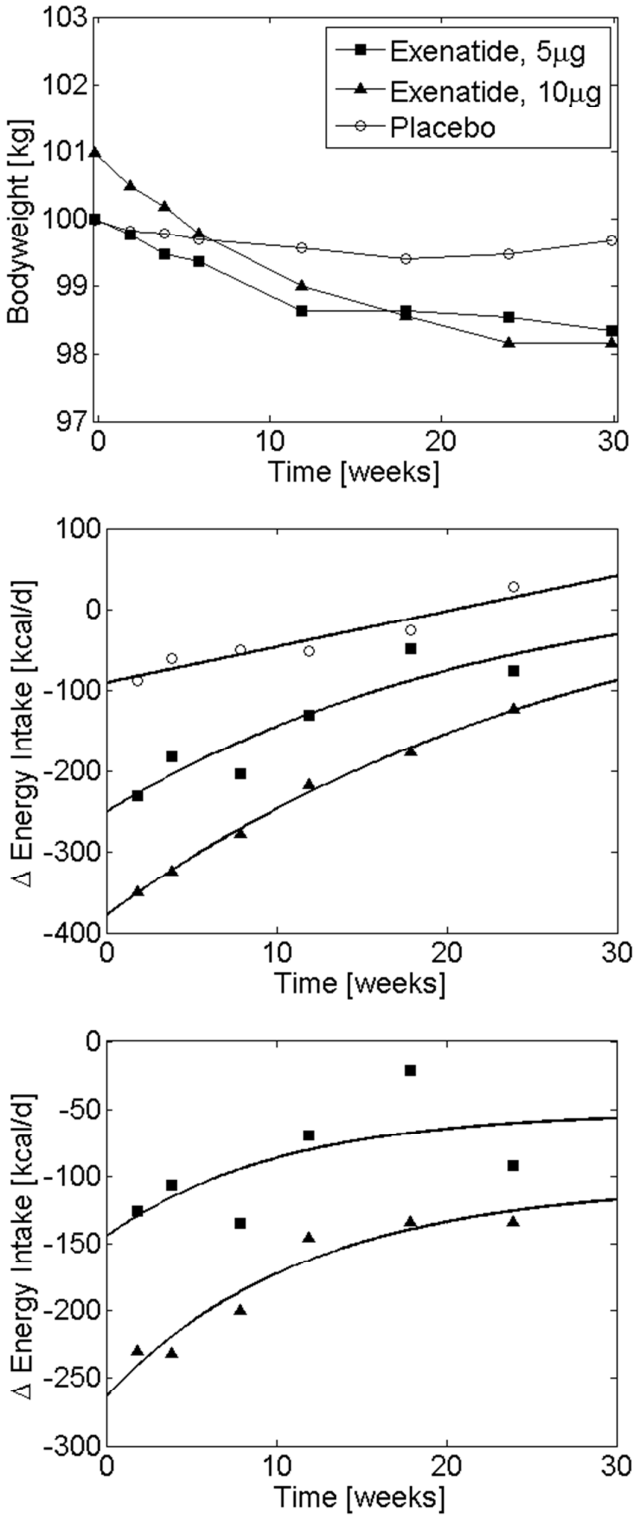

Exenatide, 5µg
Exenatide, 10µg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S3.**

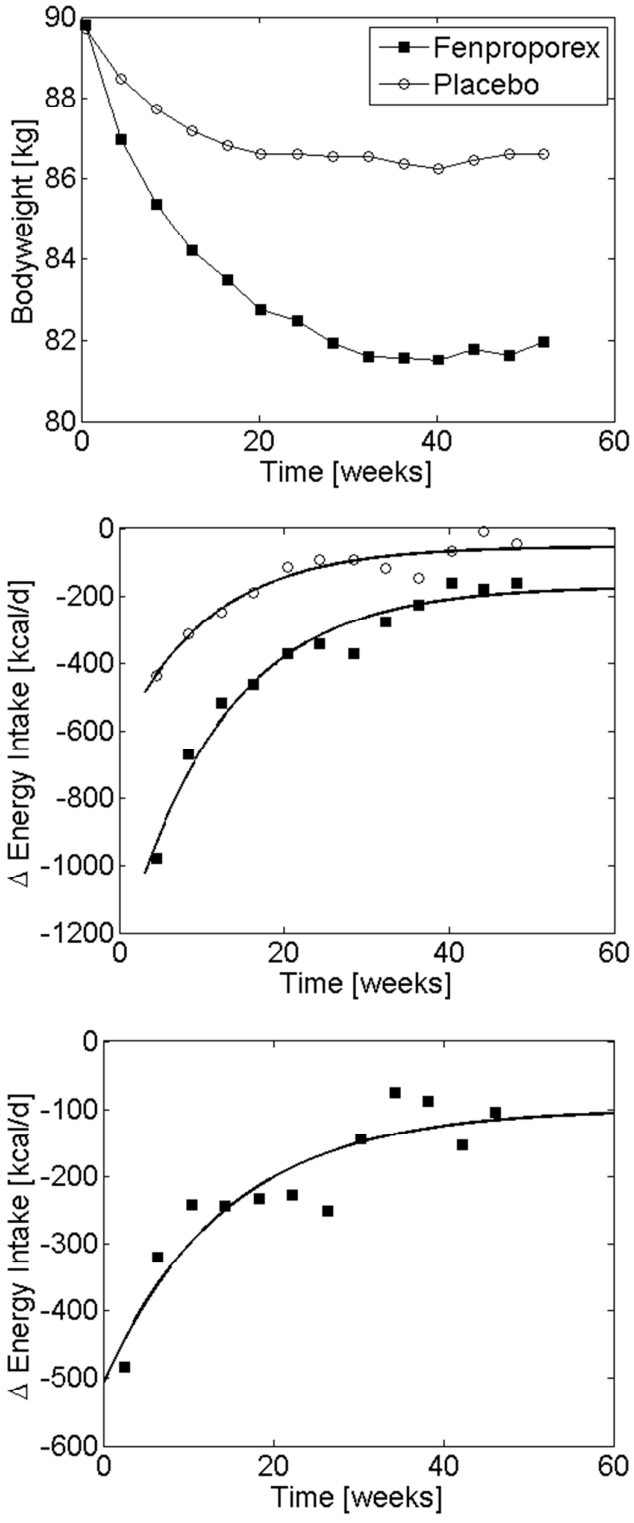

Fenproporex
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S4.**

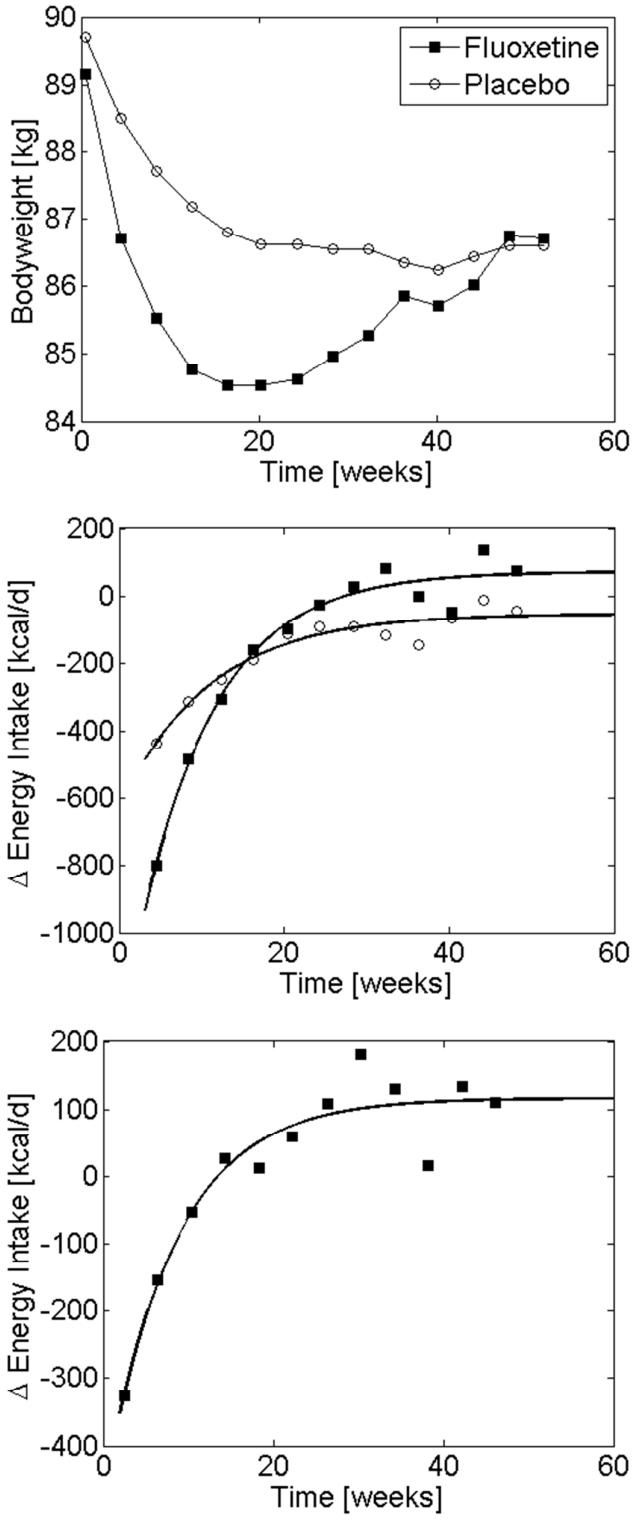
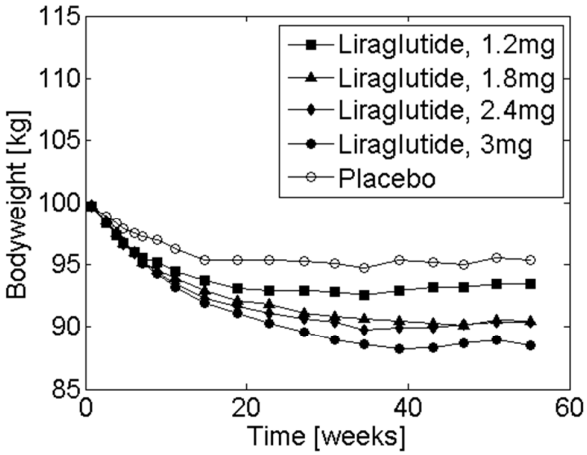
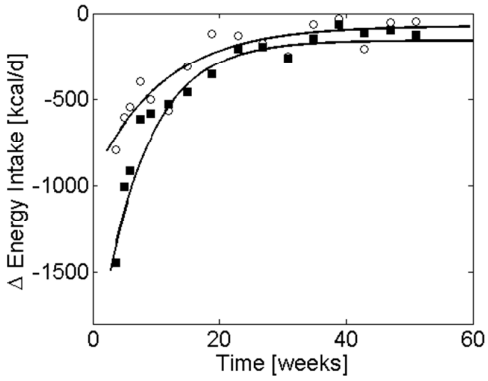
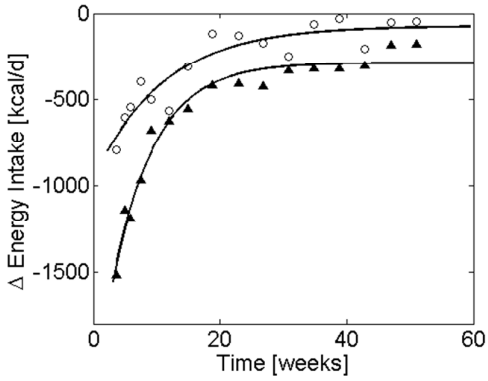
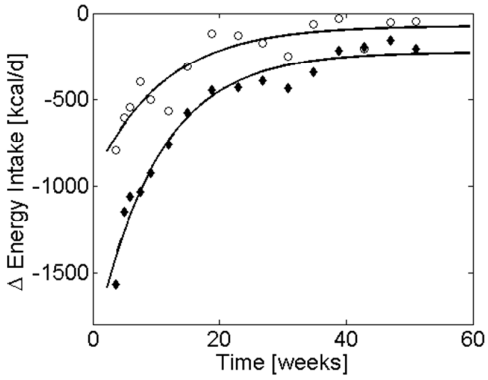

Fluoxetine
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

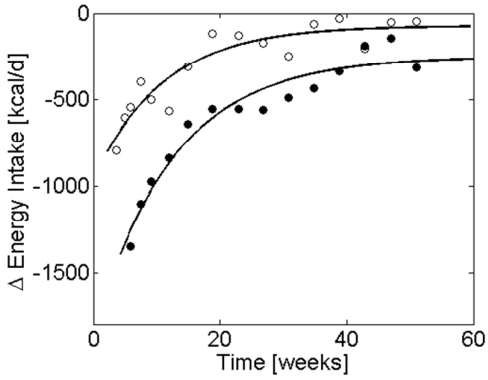
**Figure S5.**


Liraglutide, 1.2mg
Liraglutide, 1.8mg
Liraglutide, 2.4mg
Liraglutide, 3mg
Placebo
Bodyweight [kg]
Time [weeks]


Δ Energy Intake [kcal/d]
Time [weeks]


Δ Energy Intake [kcal/d]
Time [weeks]


Δ Energy Intake [kcal/d]
Time [weeks]


Δ Energy Intake [kcal/d]
Time [weeks]

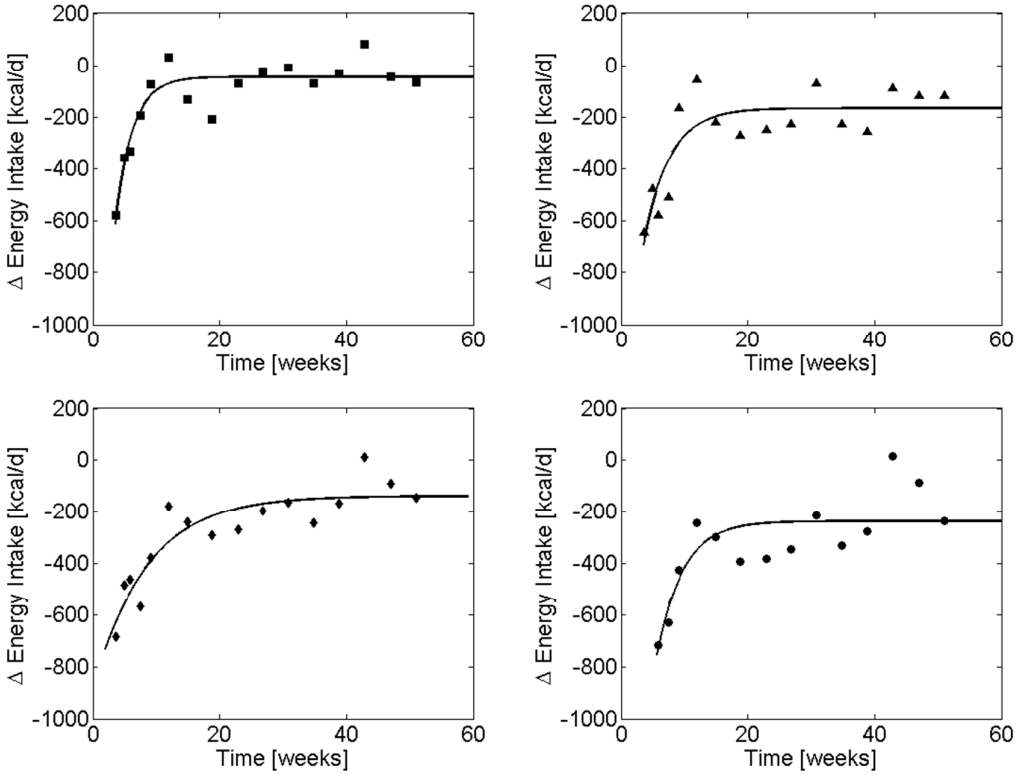

Δ Energy Intake [kcal/d]
Time [weeks]
200
0
-200
-400
-600
-800
-1000
0
20
40
60

**Figure S6.**

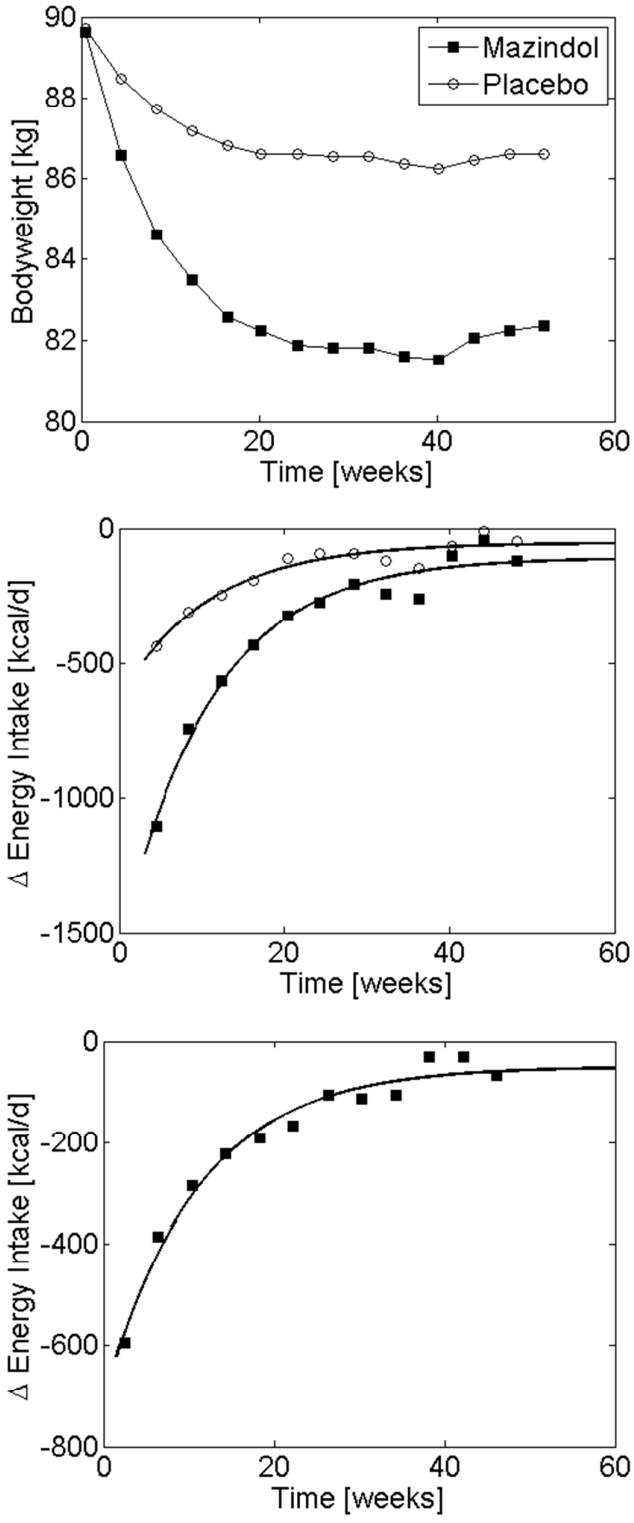

Mazindol
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S7.**

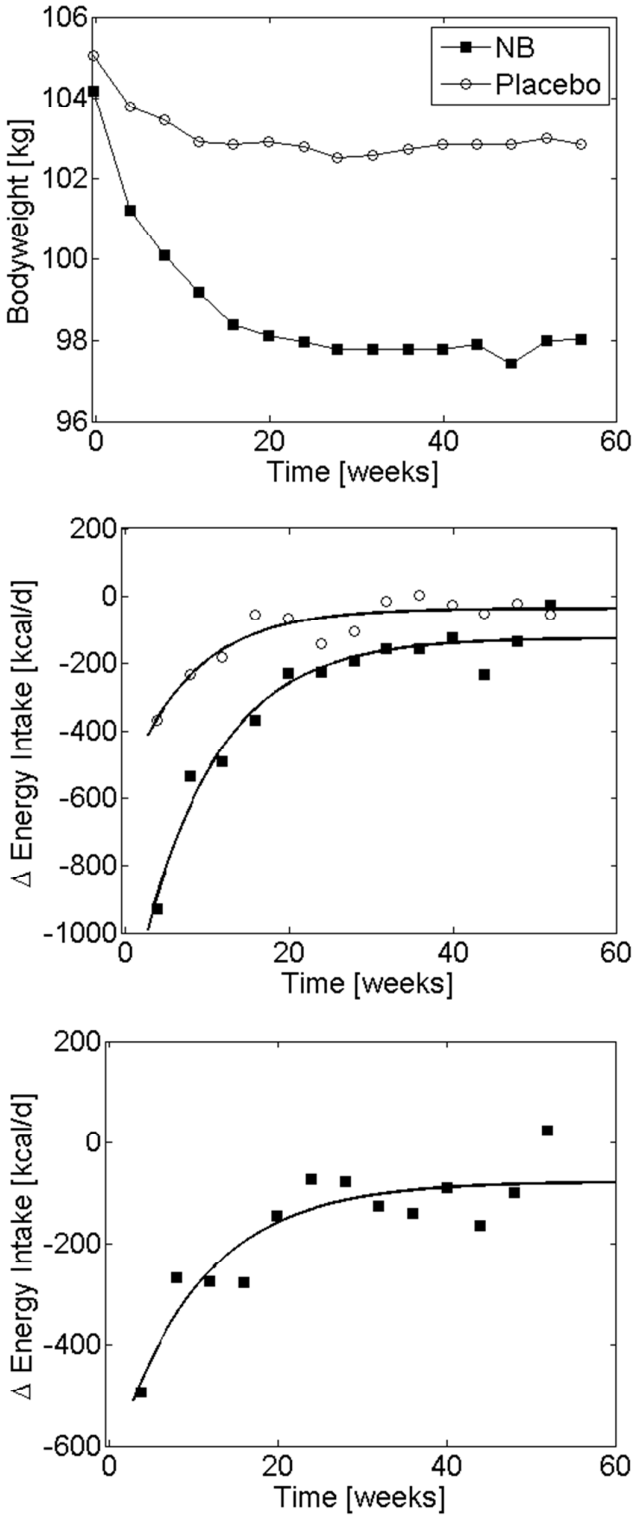

106
104
102
100
98
96
Bodyweight [kg]
NB
Placebo
0
20
40
60
Time [weeks]
200
0
-200
-400
-600
-800
-1000
Δ Energy Intake [kcal/d]
0
20
40
60
Time [weeks]
200
0
-200
-400
-600
Δ Energy Intake [kcal/d]
0
20
40
60
Time [weeks]

**Figure S8.**

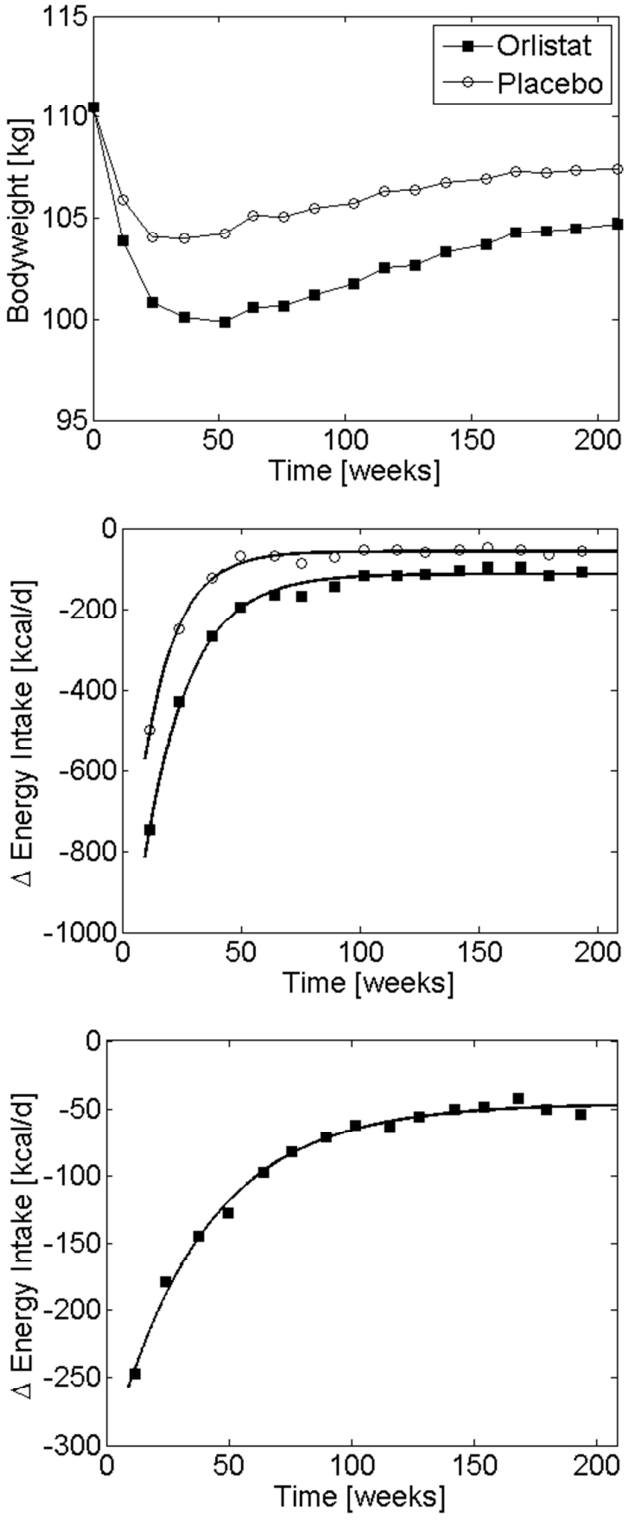

Orlistat
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S9.**

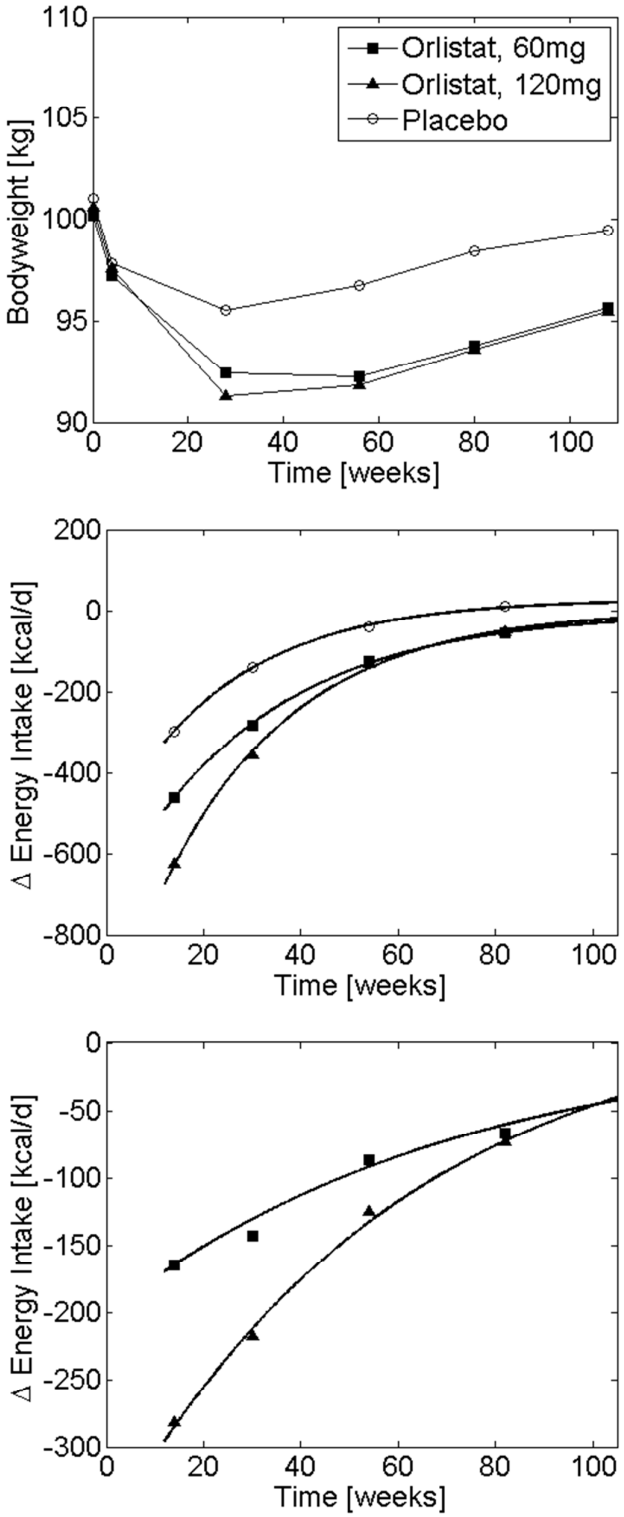

Orlistat, 60mg
Orlistat, 120mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S10.**

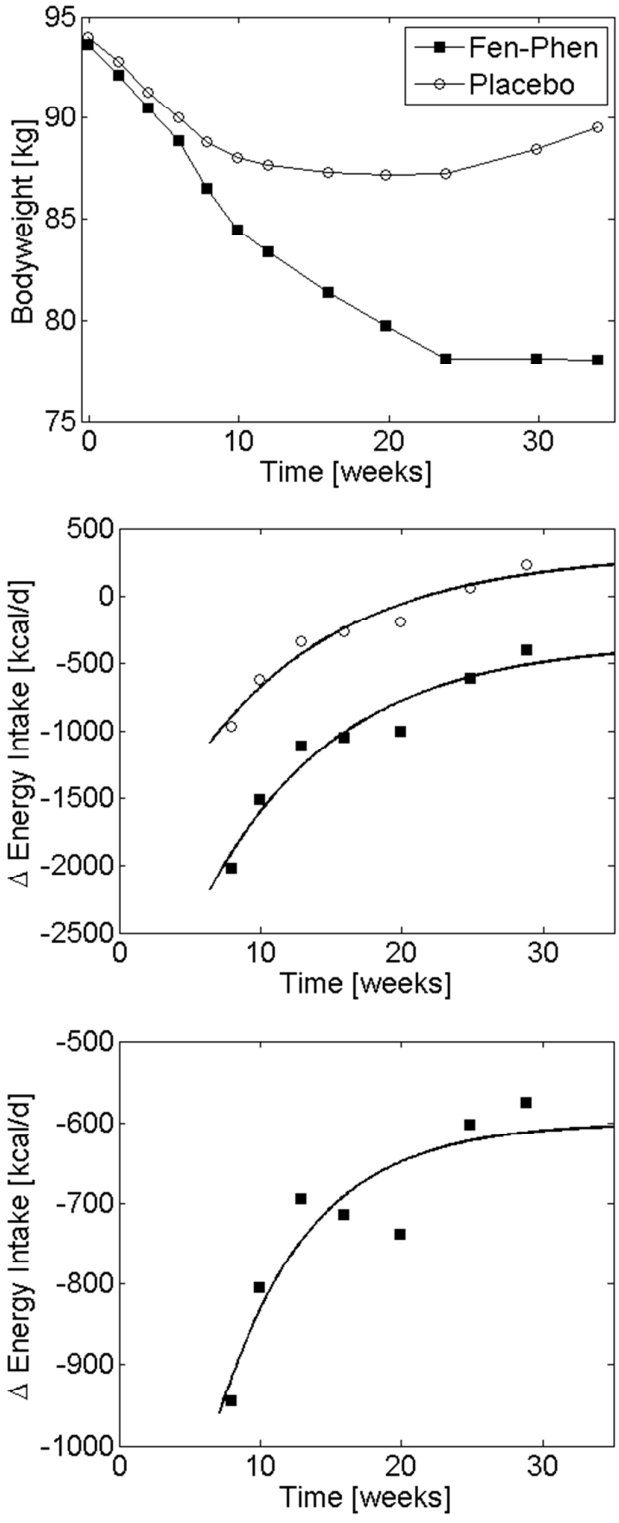

Fen-Phen
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S11.**

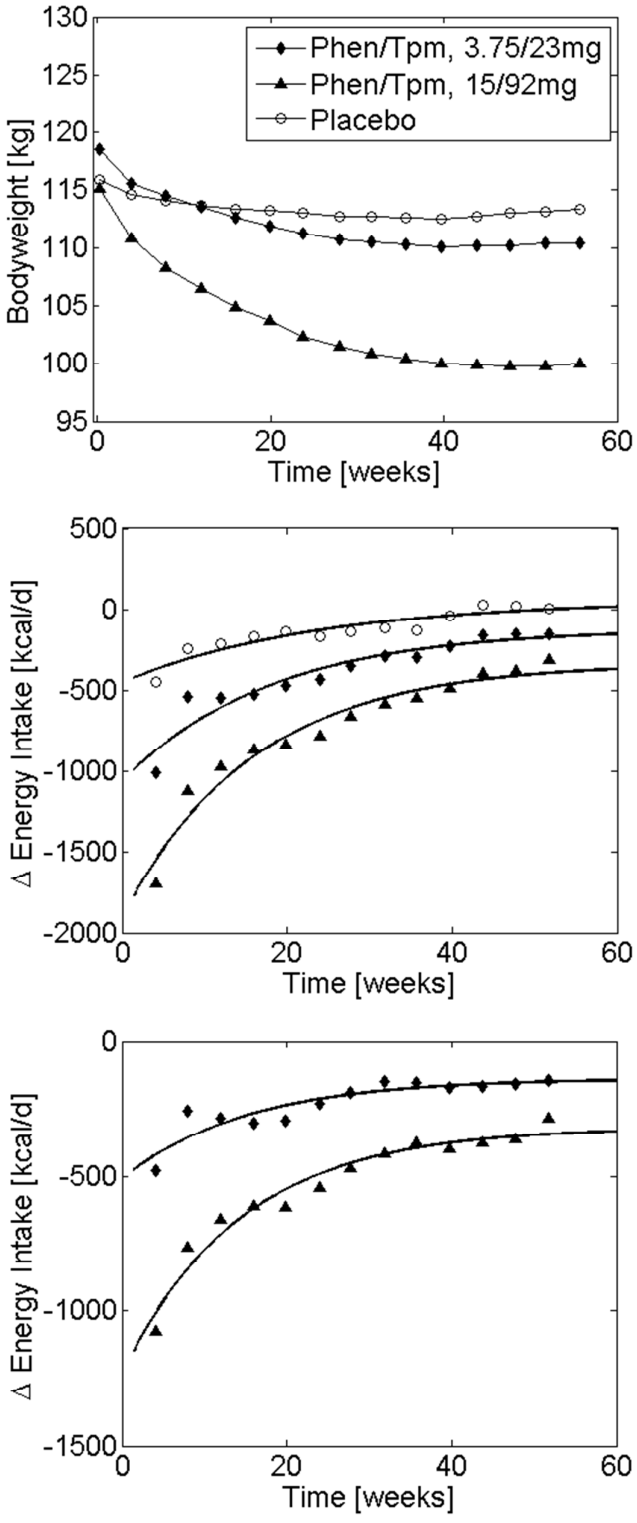

Phen/Tpm, 3.75/23mg
Phen/Tpm, 15/92mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S12.**

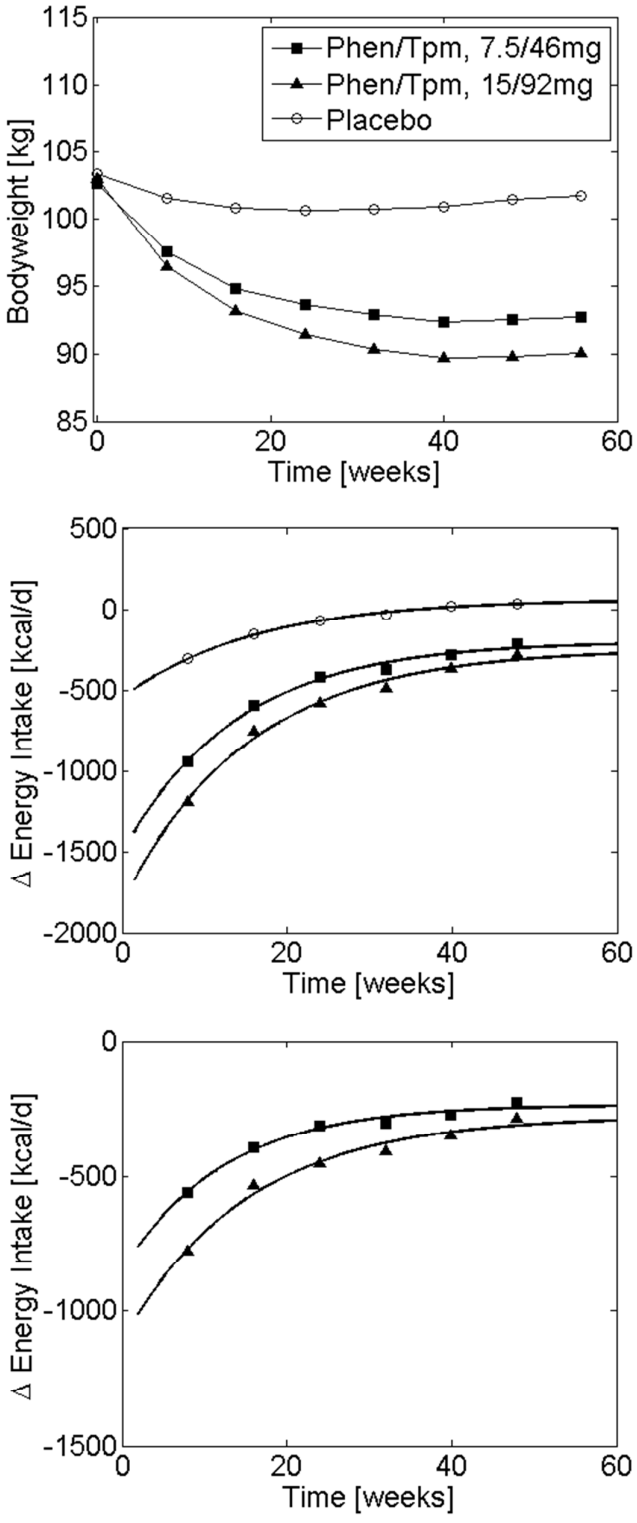

Phen/Tpm, 7.5/46mg
Phen/Tpm, 15/92mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S13.**

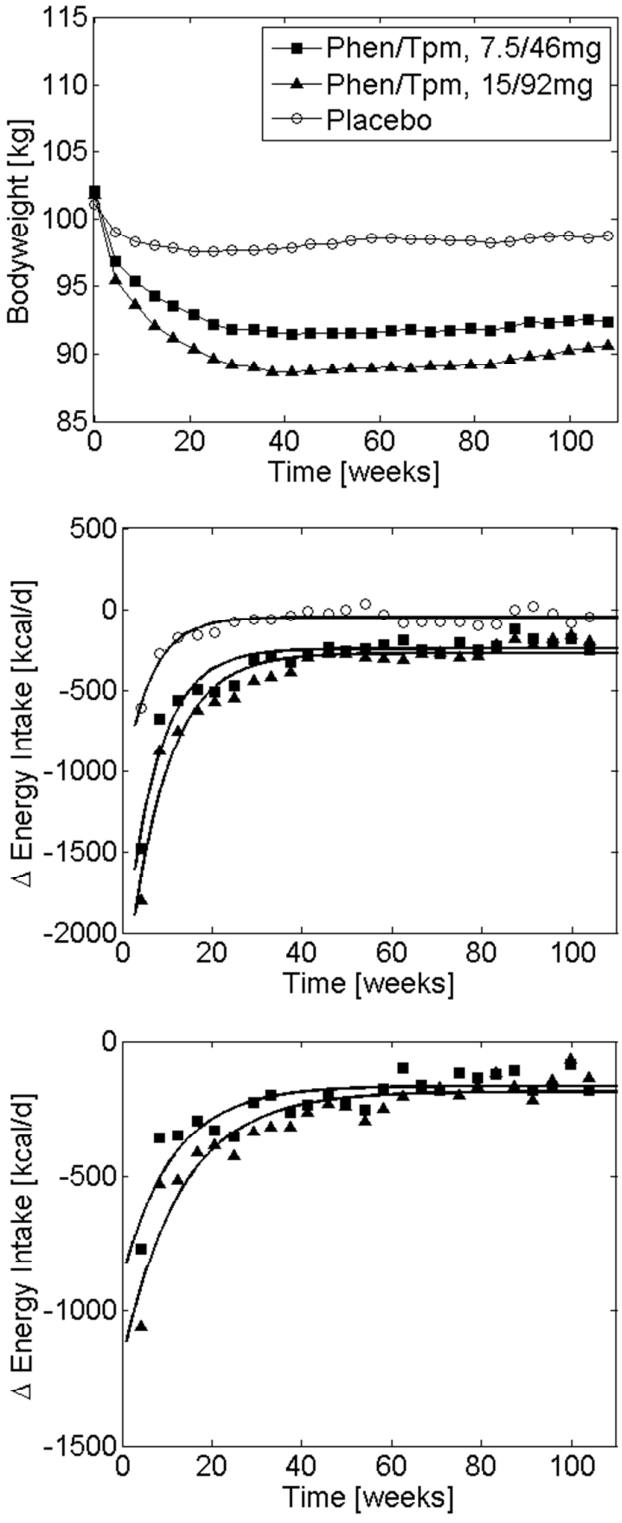

Phen/Tpm, 7.5/46mg
Phen/Tpm, 15/92mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S14.**

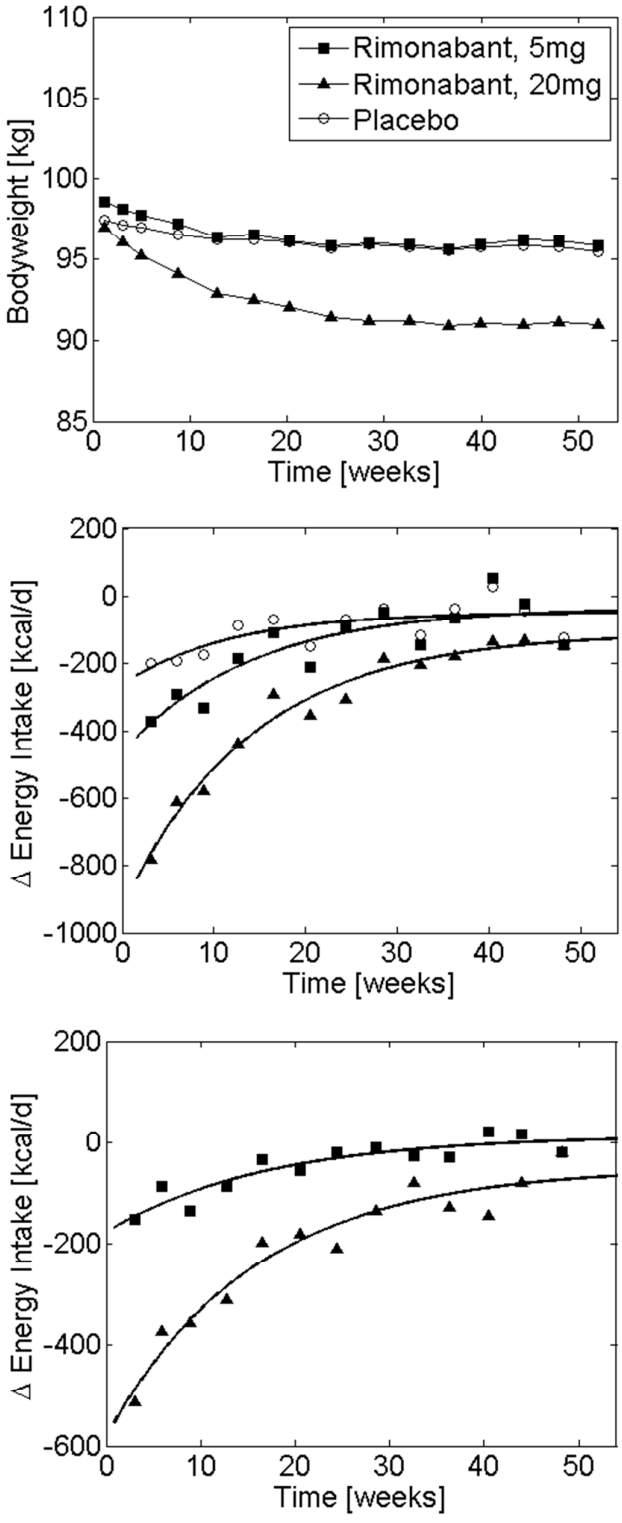

Rimonabant, 5mg
Rimonabant, 20mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S15.**

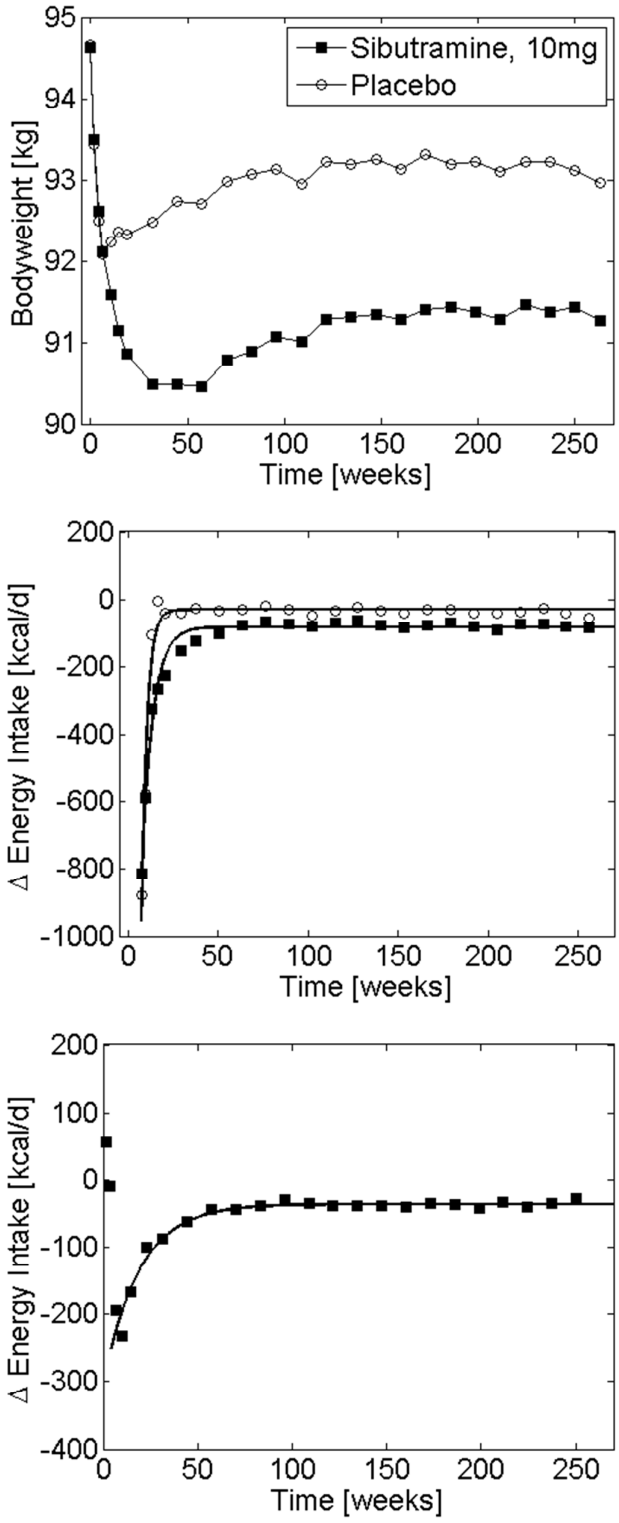

Sibutramine, 10mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S16.**

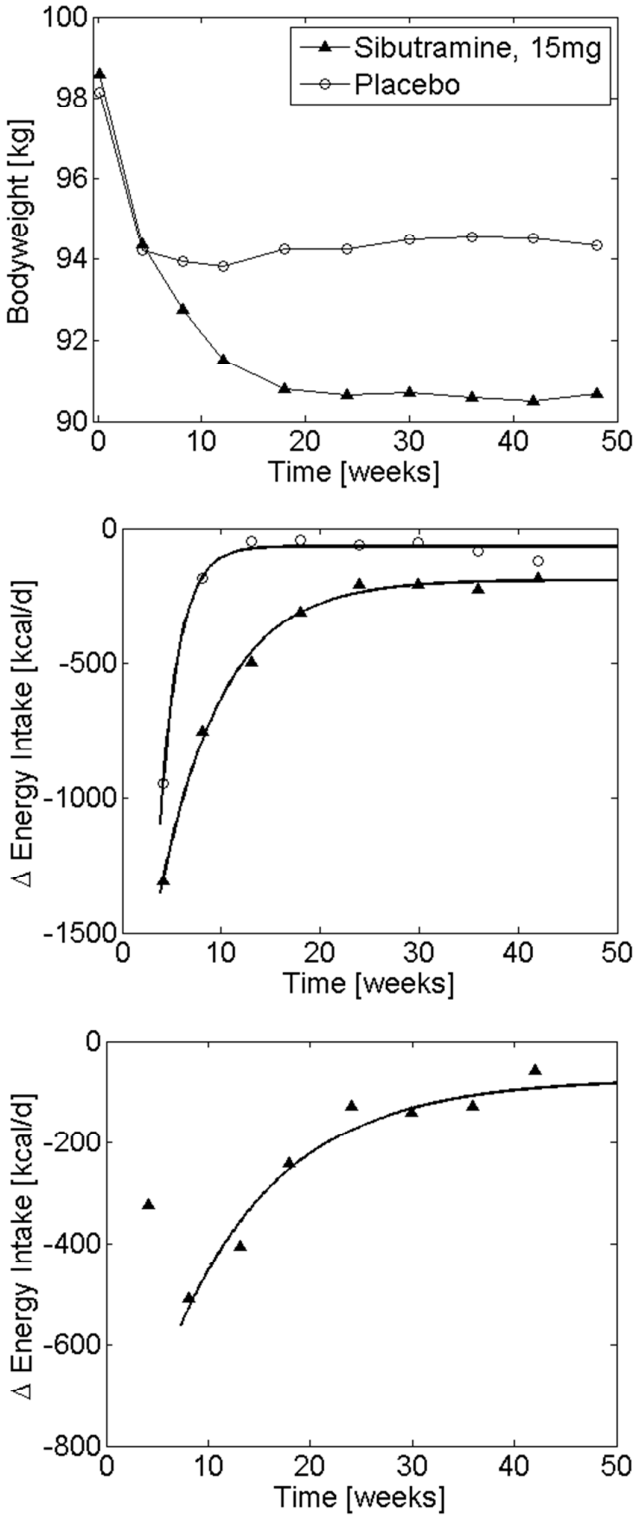

Sibutramine, 15mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S17.**

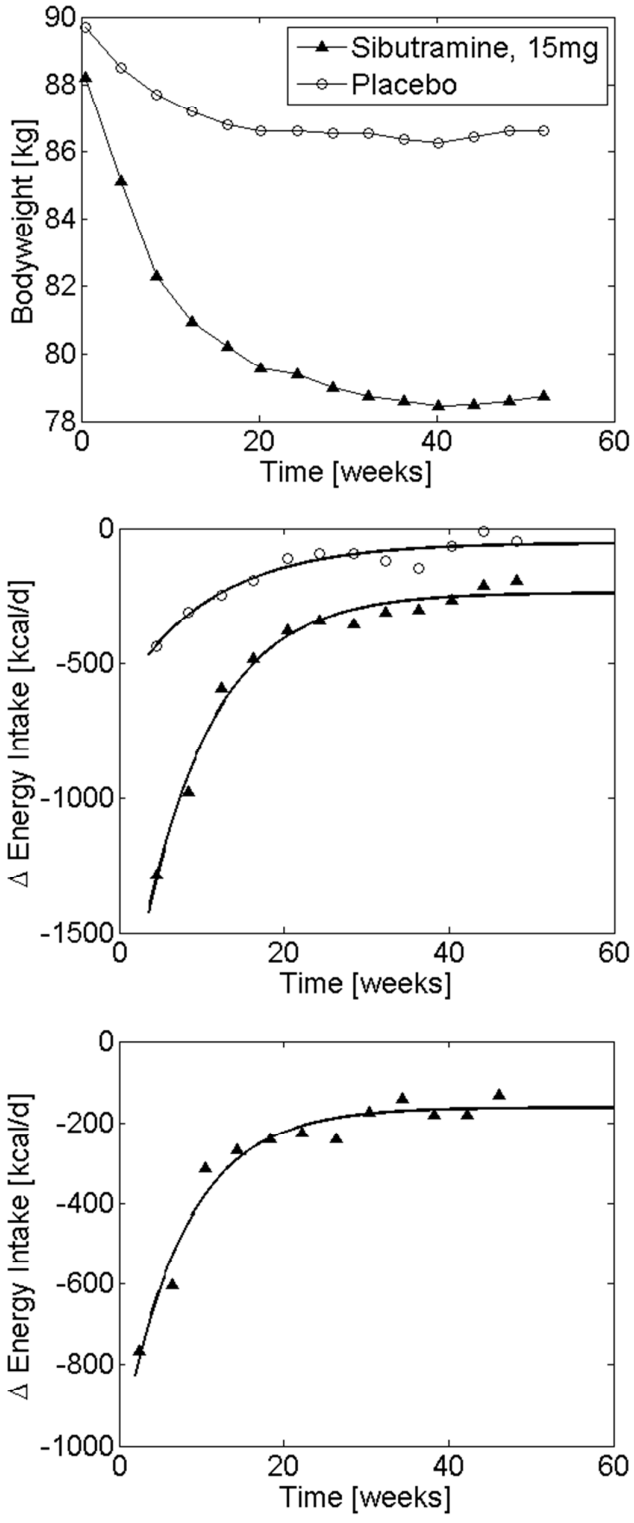

Sibutramine, 15mg
Placebo
Bodyweight [kg]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]
Δ Energy Intake [kcal/d]
Time [weeks]

**Figure S18.**

| Drug | $p_{early}$ [kcal/d] | τ [d] | $p_{late}$ [kcal/d] | $R^2$ | Duration [weeks] | Dose [mg] | Ref. |
|---|---|---|---|---|---|---|---|
| **Dexfenfluramine** | 850 | 50 | 269 | 0.81 | 52 | 15 | (18) |
| **Diethylpropion Fenproporex Fluoxetine Mazindol Sibutramine** | 386 | 78 | 47 | 0.93 | 52 | DEP: 75, FPX: 25 FXT: 20, MZD: 2, SIB: 15 | (21) |
| **Exenatide*** | - | - | - | - | 30 | 0.005, 0.01 | (12) |
| **Liraglutide** | 653 | 64 | 48 | 0.88 | 52 | 1.2, 1.8, 2.4, 3 | (11) |
| **Lorcaserin** | 528 | 78 | 40 | 0.94 | 104 | 10 | (20) |
| **Naltrexone + Bupropion** | 309 | 55 | 32 | 0.87 | 56 | N/B 32/360 | (16) |
| **Orlistat** | 492 | 99 | 57 | 0.99 | 208 | 120 | (22) |
| | 261 | 174 | -26 | 0.99 | 104 | 60 | (15) |
| | 306 | 138 | -32 | 0.99 | 104 | 120 | (15) |
| **Phentermine + Fenfluramine** | 690 | 80 | -411 | 0.96 | 34 | Phen/Fen 15/60 | (23) |
| **Phentermine + Topiramate** | 269 | 194 | -61 | 0.87 | 56 | PHEN/TPM 3.75/23, 15/92 | (10) |
| | 261 | 112 | -55 | 0.99 | 56 | PHEN/TPM 7.5/46, 15/92 | (13) |
| | 536 | 40 | 43 | 0.9 | 108 | PHEN/TPM 7.5/46, 15/92 | (14) |
| **Rimonabant** | 181 | 97 | 38 | 0.54 | 52 | 5, 20 | (19) |
| **Sibutramine**** | - | - | - | - | 260 | 10 | (17) |
| | 842 | 13 | 59 | 0.99 | 48 | 15 | (24) |

**Supplementary Table 1:** Parameter values defining the best-fit exponential time course of metabolizable energy intake in placebo groups alone. *The calculated changes in metabolizable energy intake for the placebo group in the Exenatide trial decreased linearly in time. **Calculated changes in energy intake in the placebo group in this Sibutramine trial were approximately constant.

| Drug | $p_{early}$ [kcal/d] | τ [d] | $p_{late}$ [kcal/d] | $R^2$ | Duration [weeks] | Dose [mg] | Ref. |
|---|---|---|---|---|---|---|---|
| **Dexfenfluramine** | 1269 | 44 | 228 | 0.86 | 52 | 15 | (18) |
| **Diethylpropion** | 899 | 109 | 185 | 0.96 | 52 | 75 | (21) |
| **Exenatide** | 201 | 163 | -46 | 0.85 | 30 | 0.005 | (12) |
| | 310 | 207 | -70 | 0.99 | 30 | 0.01 | (12) |
| **Fenproporex** | 827 | 88 | 151 | 0.97 | 52 | 25 | (21) |
| **Fluoxetine** | 709 | 66 | -66 | 0.97 | 52 | 20 | (21) |
| **Liraglutide** | 1147 | 59 | 213 | 0.9 | 52 | 3 | (11) |
| | 1318 | 56 | 190 | 0.98 | 52 | 2.4 | (11) |
| | 1377 | 39 | 231 | 0.96 | 52 | 1.8 | (11) |
| | 1221 | 35 | 112 | 0.95 | 52 | 1.2 | (11) |
| **Lorcaserin** | 954 | 101 | 85 | 0.94 | 104 | 10 | (20) |
| **Mazindol** | 956 | 78 | 96 | 0.97 | 52 | 2 | (21) |
| **Naltrexone + Bupropion** | 766 | 63 | 108 | 0.95 | 56 | N/B 32/360 | (16) |
| **Orlistat** | 728 | 136 | 112 | 0.99 | 208 | 120 | (22) |
| | 409 | 220 | 2 | 0.99 | 104 | 60 | (15) |
| | 556 | 191 | -3 | 0.99 | 104 | 120 | (15) |
| **Phentermine + Fenfluramine** | 1560 | 73 | 165 | 0.94 | 34 | Phen/Fen 15/60 | (23) |
| **Phentermine + Topiramate** | 615 | 143 | 72 | 0.91 | 56 | PHEN/TPM 3.75/23 | (10) |
| | 1131 | 127 | 227 | 0.96 | 56 | PHEN/TPM 15/92 | (10) |
| | 805 | 97 | 174 | 0.99 | 56 | PHEN/TPM 7.5/46 | (13) |
| | 1010 | 107 | 213 | 0.99 | 56 | PHEN/TPM 15/92 | (13) |
| | 1262 | 44 | 219 | 0.92 | 108 | PHEN/TPM 7.5/46 | (14) |
| | 1523 | 54 | 246 | 0.92 | 108 | PHEN/TPM 15/92 | (14) |
| **Rimonabant** | 321 | 110 | 22 | 0.73 | 52 | 5 | (19) |
| | 649 | 114 | 81 | 0.96 | 52 | 20 | (19) |
| **Sibutramine** | 173 | 111 | 13 | 0.98 | 260 | 10 | (17) |
| | 1158 | 43 | 172 | 0.99 | 48 | 15 | (24) |
| | 1161 | 61 | 214 | 0.98 | 52 | 15 | (21) |

**Supplementary Table 2:** Parameter values defining the best-fit exponential time course of metabolizable energy intake in treatment groups alone.