**Supplemental Digital Content Table 1. Dietary Intake, Stool Fat Absorption, Plasma Fatty Acids by Placebo and LYM-X-SORB (LXS) at Baseline, 3 and 12 Months**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Time Points** |  | **Effect of treatment**  |
|  | **Baseline** | **3 month** | **12 month** |  | **P0-33** | **P0-3-124** |
| **DIETARY INTAKE AND FAT ABSORPTION** |  |  |  |  |
| **Estimated Energy Requirement, %1,5** |  |  |  |  |  |
|  Placebo | 119 ± 352 | 123 ± 29 | 123 ± 31 |  | 0.87 | 0.96 |
|  LXS | 119 ± 26 | 123 ± 23 | 124 ± 27 |  |  |  |
| **Fat, g1,5** |  |  |   |  |  |  |
|  Placebo | 98 ± 40 | 102 ± 30 | 106 ± 32 |  | 0.86 | 0.57 |
|  LXS | 97 ± 29 | 99 ± 34 | 105 ± 36 |  |  |  |
| **Fat, %kcal5** |  |  |   |  |  |  |
|  Placebo | 36 ± 6 | 35 ± 6 | 36 ± 4 |  | 0.79 | 0.36 |
|  LXS | 36 ± 5 | 34 ± 7 | 35 ± 5 |  |  |  |
| **Pancreatic Enzymes, Lipase Units1,6** |  |  |  |  |  |
|  Placebo | 315,938 ± 129,583 | 327,870 ± 126,817 | 340,410 ± 123,118 |  | 0.80 | 0.48 |
|  LXS | 288,062 ± 123,885 | 289,709 ± 128,251 | 264,533 ± 97,713 |  |  |  |
| **Coefficient of Fat Absorption, % 7** |  |  |  |  |  |
|  Placebo | 84 ± 12 | 85 ± 19 | 88 ± 11 |  | 0.16 | 0.34 |
|  LXS | 82 ± 11 | 88 ± 7\*\* | 87 ± 8\*\* |  |  |  |
| **Saturated Fatty Acids, %kcal5** |  |  |  |  |  |
|  Placebo | 13.3 ± 3.2 | 12.7 ± 2.9 | 13.2 ± 2.7 |  | 0.15 | 0.12 |
|  LXS | 13.9 ± 3.0 | 12.2 ± 3.1\*\*\* | 12.1 ± 3.3\*\* |  |  |  |
| **Monounsaturated Fatty Acids, %kcal1,5** |  |  |  |  |  |
|  Placebo | 12.6 ± 2.9 | 11.5 ± 2.6\*\* | 12.3 ± 2.2 |  | 0.40 | 0.69 |
|  LXS | 12.1 ± 2.3 | 11.6 ± 3.3 | 11.9 ± 2.5 |  |  |  |
| **Polyunsaturated Fatty Acids, %kcal1,5** |  |  |  |  |  |
|  Placebo | 7.0 ± 2.5 | 8.1 ± 2.3\*\* | 8.2 ± 1.9 |  | 0.41 | 0.38 |
|  LXS | 7.2 ± 1.7 | 8.1 ± 2.3\* | 8.1 ± 1.7\* |  |  |  |
| **Linoleic Acid, g1.5** |  |  |  |  |  |  |
|  Placebo | 17.6 ± 11.7 | 20.7 ± 9.2 | 21.3 ± 9.3 |  | 0.70 | 0.50 |
|  LXS | 17.7 ± 7.0 | 20.9 ± 9.4 | 21.3 ± 7.6 |  |  |  |
| **Supplemental Digital Content Table 1. Continued** |  |  |  |  |
| **PLASMA FATTY ACIDS, nmol/L8** |  |  |  |  |  |
| **Lauric (C12:0)1** |  |  |  |  |  |  |
|  Placebo3 | 23 ± 15 | 21 ± 12 | 24 ± 19 |  | 0.035 | 0.039 |
|  LXS4 | 19 ± 12 | 34 ± 55\* | 22 ± 23 |  |  |
| **Myristic (C14:0)1** |  |  |  |  |  |  |
|  Placebo  | 148 ± 73 | 153 ± 66 | 162 ± 80 |  | 0.029 | 0.080 |
|  LXS | 132 ± 56 | 196 ± 156\*\* | 170 ± 114\* |  |  |
| **Hexadecenoic (C16:1ω9)1** |  |  |  |  |  |
|  Placebo  | 42 ± 21 | 39 ± 14 | 39 ± 15 |  | 0.039 | 0.073 |
|  LXS | 39 ± 16 | 47 ± 22\*\* | 46 ± 19\* |  |  |
| **Palmitoleic (C16:1ω7)** |  |  |  |  |  |
|  Placebo  | 243 ± 154 | 221 ± 101 | 236 ± 116 |  | 0.003 | 0.009 |
|  LXS | 214 ± 105 | 299 ± 186\*\*\* | 292 ± 173\*\* |  |  |  |
| **Palmitic (C16:0)1** |  |  |  |  |  |  |
|  Placebo  | 2267 ± 633 | 2275 ± 650 | 2329 ± 624 |  | 0.020 | 0.054 |
|  LXS | 2062 ± 464 | 2560 ± 1191\*\* | 2436 ± 899\*\* |  |  |  |
| **ɣ-linolenic (C18:3ω6)1** |  |  |  |  |  |
|  Placebo  | 69 ± 30 | 75 ± 39 | 77 ± 33 |  | 0.041 | 0.11 |
|  LXS | 63 ± 26 | 92 ± 61\*\* | 89 ± 50\*\* |  |  |  |
| **α-Linolenic Acid (C18:3ω3)1** |  |  |  |  |  |
|  Placebo  | 52 ± 26 | 61 ± 30 | 62 ± 26\*\* |  | 0.13 | 0.29 |
|  LXS | 49 ± 21 | 69 ± 37\*\*\* | 67 ± 34\*\*\* |  |  |  |
| **Linoleic Acid (C18:2ω6)** |  |  |  |  |  |
|  Placebo  | 2333 ± 491 | 2380 ± 552 | 2358 ± 500  |  | 0.069 | 0.15 |
|  LXS | 2230 ± 528 | 2522 ± 754\*\* | 2405 ± 571\* |  |  |  |
| **Oleic (C18:1ω9)1** |  |  |  |  |  |  |
|  Placebo  | 1872 ± 557 | 1798 ± 488 | 1839 ± 490 |  | 0.017 | 0.046 |
|  LXS | 1762 ± 367 | 2068 ± 775\*\* | 1997 ± 589\* |  |  |  |
| **­ Vaccenic (C18:1ω7)1** |  |  |  |  |  |  |
|  Placebo  | 259 ± 92 | 243 ± 96 | 249 ± 103 |  | 0.10 | 0.26 |
|  LXS | 245 ± 81 | 280 ± 122 | 269 ± 129 |  |  |  |
|  |  |  |  |  |  |  |
| **Supplemental Digital Content Table 1. Continued** |  |  |  |  |
| **Stearic (C18:0)1** |  |  |  |  |  |  |
|  Placebo  | 808 ± 169 | 825 ± 213 | 843 ± 196 |  | 0.16 | 0.36 |
|  LXS | 750 ± 133 | 859 ± 317\* | 812 ± 263 |  |  |  |
| **Eicosapentaenoic (C20:5ω3)1** |  |  |  |  |  |
|  Placebo  | 39 ± 21 | 50 ± 31\*\* | 46 ± 21 |  | 0.59 | 0.86 |
|  LXS | 37 ± 23 | 42 ± 18 | 41 ± 22 |  |  |  |
| **Arachidonic (C20:4ω6)** |  |  |  |  |  |
|  Placebo  | 454 ± 143 | 432 ± 129 | 458 ± 138 |  | 0.023 | 0.047 |
|  LXS | 430 ± 127 | 463 ± 161 | 460 ± 143\*\* |  |  |  |
| **Mead Acid (C20:3ω9)1** |  |  |  |  |  |
|  Placebo  | 23 ± 10 | 21 ± 7 | 21 ± 7 |  | 0.091 | 0.20 |
|  LXS | 22 ± 12 | 23 ± 7 | 22 ± 9 |  |  |  |
| **Homo-ɣ-linolenic (C20:3ω6)** |  |  |  |  |  |
|  Placebo  | 136 ± 42 | 133 ± 33 | 134 ± 32 |  | 0.46 | 0.76 |
|  LXS | 126 ± 33 | 132 ± 46 | 129 ± 39 |  |  |  |
| **Arachidic (C20:0)** |  |  |  |  |  |  |
|  Placebo  | 26 ± 4 | 26 ± 5 | 27 ± 5 |  | 0.46 | 0.75 |
|  LXS | 26 ± 4 | 27 ± 4 | 27 ± 5 |  |  |  |
| **Docosahexaenoic (C22:6ω3)1** |  |  |  |  |  |
|  Placebo  | 62 ± 23 | 64 ± 34 | 67 ± 32 |  | 0.89 | 0.83 |
|  LXS | 61 ± 26 | 62 ± 37 | 63 ± 26 |  |  |  |
| **19-Docosapentaenoic (C22:5ω6)1** |  |  |  |  |  |
|  Placebo  | 20 ± 8 | 17 ± 6\*\* | 17 ± 7\* |  | 0.026 | 0.055 |
|  LXS | 18 ± 6 | 20 ± 9 | 20 ± 10 |  |  |  |
| **Docosapentanoic (C22:5ω3)1** |  |  |  |  |  |
|  Placebo  | 39 ± 16 | 42 ± 18 | 41 ± 13 |  | 0.15 | 0.28 |
|  LXS | 35 ± 13 | 44 ± 19\*\* | 41 ± 17\*\* |  |  |  |
| **Docosatetranoic (C22:4ω6)1** |  |  |  |  |  |
|  Placebo  | 25 ± 9 | 23 ± 8 | 23 ± 8 |  | 0.012 | 0.037 |
|  LXS | 22 ± 7 | 28 ± 13\*\* | 26 ± 11\*\* |  |  |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Supplemental Digital Content Table 1. Continued** |  |  |  |  |
| **Docosanoic (C22:1)** |  |  |  |  |  |  |
|  Placebo  | 6.4 ± 1.8 | 5.8 ± 1.2 | 6.0 ± 1.4 |  | 0.062 | 0.17 |
|  LXS | 6.1 ± 1.4 | 6.3 ± 1.3 | 6.0 ± 2.0 |  |  |  |
| **Nervonic (C24:1ω9)1** |  |  |  |  |  |  |
|  Placebo  | 68 ± 17 | 64 ± 15 | 66 ± 18 |  | 0.61 | 0.78 |
|  LXS | 68 ± 14 | 66 ± 14 | 69 ± 19 |  |  |  |
| **Triene:Tetraene ratio1** |  |  |  |  |  |  |
|  Placebo  | 0.05 ± 0.02 | 0.05 ± 0.01 | 0.05 ± 0.01\* |  | 0.90 | 0.97 |
|  LXS | 0.05 ± 0.02 | 0.05 ± 0.02 | 0.05 ± 0.01 |  |  |  |
| **PLASMA FATTY ACID GROUP, mmol/L8** |
| **Saturated1**  |  |  |  |  |  |  |
|  Placebo  | 3.38 ± 0.86 | 3.40 ± 0.94 | 3.49 ± 0.87 |  | 0.022 | 0.069 |
|  LXS | 3.10 ± 0.64 | 3.80 ± 1.72\*\* | 3.61 ± 1.27\* |  |  |  |
| **Monounsaturated1** |  |  |  |  |  |
|  Placebo  | 2.51 ± 0.81 | 2.39 ± 0.68 | 2.46 ± 0.67 |  | 0.014 | 0.043 |
|  LXS | 2.35 ± 0.52 | 2.80 ± 1.07\*\* | 2.69 ± 0.88\* |  |  |  |
| **Polyunsaturated**  |  |  |  |  |  |
|  Placebo  | 3.25 ± 0.72 | 3.31 ± 0.79 | 3.32 ± 0.65 |  | 0.058 | 0.12 |
|  LXS | 3.09 ± 0.70 | 3.49 ± 1.05\*\* | 3.36 ± 0.83\* |  |  |  |
| **Total Fatty Acids1** |  |  |  |  |  |  |
|  Placebo  | 9.16 ± 2.18 | 9.12 ± 2.26 | 9.30 ± 2.00 |  | 0.015 | 0.046 |
|  LXS | 8.56 ± 1.64 | 10.14 ± 3.63\*\* | 9.70 ± 2.83\*\* |  |  |  |
| **SERUM TRIGLYCERIDES AND CHOLESTEROL, mg/dL1,9** |  |  |  |  |
| **Triglycerides** |  |  |  |  |  |  |
|  Placebo | 87 ± 37 | 91 ± 20 |  100± 54 |  | 0.022 | 0.049 |
|  LXS | 84 ± 40 | 107 ± 58\*\* | 110 ± 56\*\* |  |  |  |
| **Total Cholesterol** |  |  |  |  |  |  |
|  Placebo | 134 ± 27 | 138 ± 29 |  133± 25 |  | 0.66 | 0.70 |
|  LXS | 132 ± 19 | 138 ± 25 | 137 ± 24 |  |  |  |

Triene:Tetraene Ratio, Mead Acid: Arachidonic Acid.

**­­­­­­­­­­­­­­­­**1 Log transformation was applied for skewed variables in the mixed models

**Supplemental Digital Content Table 1. Continued**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

2 Mean ± SD (all such values)

3 P0-3 is testing for partial randomization group × time interaction between baseline and 3 month from a mixed effects linear regression model that included baseline, 3, and 12 months data (i. randomization group × time interaction was used).

4 P0-3-12 is testing for randomization group × time interaction between baseline and 3, and 12 month.

5 n=54, 37, and 35 for Placebo group, and n=44, 31, and 23 for LXS group at baseline, 3, and 12 months, respectively.

6 n=56, 46, and 39 for Placebo group, and n=54, 40, and 30 for LXS group at baseline, 3, and 12 months, respectively.

7 n=41, 36, and 30 for Placebo group, and n=35, 27, and 20 for LXS group at baseline, 3, and 12 months, respectively.

8 n=56, 46, and 39 for Placebo group, and n=51, 40, and 31 for LXS group at baseline, 3, and 12 months, respectively.

9 n=55, 46, and 39 for Placebo group, and n=52, 39, and 31 for LXS group at baseline, 3, and 12 months, respectively.

\*(P<0.05) \*\*(P<0.01) \*\*\*(P<0.001) difference from baseline within randomization group.

**Supplemental Digital Content Table 2. Change in plasma total fatty acid (Δ Total FA) and linoleic acid status (Δ LA) predicting change in clinical outcomes over 3 and 12 months in subjects who completed the study**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Δ Total FA (mmol/L)** |  | **Δ LA (mmol/L)** |
| **Outcome** | **Coefficient** | **SE** | **P** |  | **Coefficient** | **SE** | **P** |
| Weight-age z score | 0.02 | 0.01 | 0.13 |  | 0.10 | 0.05 | 0.042 |
| Height-age z score | -0.01 | 0.01 | 0.32 |  | -0.03 | 0.03 | 0.38 |
| BMI-age z score | 0.04 | 0.02 | 0.011 |  | 0.21 | 0.07 | 0.003 |
| Fat free mass, kg | 0.19 | 0.07 | 0.005 |  | 0.57 | 0.31 | 0.064 |
| Fat mass, kg | 0.05 | 0.04 | 0.30 |  | 0.340 | 0.17 | 0.092 |
| Fat, % | 0.08 | 0.09 | 0.41 |  | 0.71 | 0.41 | 0.085 |
| FEV1, % predicted | 0.69 | 0.49 | 0.16 |  | 3.47 | 2.24 | 0.12 |

FEV1, forced expiratory volume at 1 second

Results from regression models with ΔTotal FA (mmol/L) on left and Δ LA (mmol/L) on right predicting change from baseline in clinical outcomes over 3 and 12 months with baseline Total FA and LA in the respective models. The analyses are restricted to 69 subjects completing the 12-month study with fatty acid data at baseline and all models are adjusted for age, sex and adherence to supplement.

**Supplemental Digital Content Figure 1.** Flow diagram for subjects randomized, drop-outs and completers in the placebo-controlled 12-month trial of daily LXS supplementation in children with cystic fibrosis and pancreatic insufficiency.

**Supplemental Digital Content Figure 2**. Mean percent change from baseline in plasma fatty acids by randomization group at 3 months (left graph) and 12 months (right graph). The error bars represent ± standard error of the mean. Samples sizes are 46 and 39 for Placebo and 40 and 31 for LXS group, at 3 and 12 months, respectively. The percent change at 3 months for Total FA and MUFA was significantly different between randomization groups by Wilcoxon rank-sum test at p<0.05 level (marked by asterisks). LA, linoleic acid; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; Total FA, total fatty acids.

**Supplemental Digital Content Figure 1**



**Supplemental Digital Content Figure 2**

