**Supplementary Table 1. Summary of the change of individual symptoms of chronic fatigue syndrome from baseline to day 60**

|  |  | **Placebo****(n=58)** | **Low dose****(n = 58)** |  | **High dose****(n = 59)** |  | **Product effect*****p*-value** |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |
| Impaired memory or concentration  | Relief | 8 (13.8%) | 26 (44.8%) | \*\*\* | 32 (54.2) | \*\*\* | <.0001 |
| No change | 50 (86.2%) | 32 (55.2%) | 27 (45.8%) |  |
| Muscle pain | Relief | 8 (86.2%) | 25 (43.1%) | \*\*\* | 29 (49.2%) | \*\*\* | 0.0001 |
| No change | 50 (86.2%) | 33 (56.9%) | 30 (50.9%) |  |
| Unrefreshing sleep | Relief | 3 (5.2%) | 22 (37.9%) | \*\*\* | 27 (45.8%) | \*\*\* | <.0001 |
| No change | 55 (94.8%) | 36 (62.1%) | 32 (54.2%) |  |
| Post-exertional malaise | Relief | 5 (8.6%) | 22 (37.9%) | \*\*\* | 25 (42.4%) | \*\*\* | <.0001 |
| No change | 53 (91.4%) | 36 (62.1G) | 34 (57.6G) |  |
| Sore throat | Relief | 5 (8.6%) | 11 (19.0%) |  | 14 (23.7%) |  | 0.1444 |
| No change | 47 (81.0%) | 45 (77.6%) | 42 (71.2%) |  |
| Worsen | 6 (10.3%) | 2 (3.5%) | 3 (5.1%) |  |
| Tender cervical or axillary lymph nodes | Relief | 0 (0.0%) | 2 (3.5%) |  | 1 (1.7%) |  | 0.5451 |
| No change | 57 (98.3%) | 55 (94.8%) | 58 (98.3%) |  |
| Worsen | 1 (1.7%) | 1 (1.7%) | 0 (0.0%) |  |
| Multiple joint pain | Relief | 0 (0.0%) | 3 (5.2%) |  | 1 (1.7%) |  | 0.2225 |
| No change | 58 (100%) | 54 (93.1%) | 58 (98.3%) |  |
| Worsen | 0 (0.0%) | 1 (1.7%) | 0 (0.0%) |  |
| New headaches | Relief | 5 (8.6%) | 8 (13.8%) |  | 8 (13.6%) |  | 0.6828 |
| No change | 48 (82.8%) | 47 (81.0%) | 49 (83.1%) |  |
| Worsen | 5 (8.6%) | 3 (5.2%) | 2 (3.4%) |  |

Data are frequency (%). Product effect was evaluated by chi-square test. Post-hoc test with Bonferroni adjustment was applied to variables with significant group difference for further pair-wise group comparison. \*\*\**P* < 0.001 compared with placebo group.

**Supplementary Table 2. Pearson correlation coefficients between changes in blood biomarkers and changes in Chadler fatigue questionnaire scores (day 60 – baseline)**

|  | **Blood ammonia** | **Blood glucose** | **Free fatty acid** | **Creatine kinase** | **C-reactive protein** | **Blood lactic acid** | **Estradiol (female)** | **Testosterone (male)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Physical fatigue (total score)** | 0.0158 | -0.0964 | -0.1128 | 0.0187 | 0.0304 | 0.1639 | -0.0293 | -0.0184 |
| 0.8352 | 0.2043 | 0.1371 | 0.8059 | 0.6899 | 0.0302\* | 0.7825 | 0.8683 |
| 1. Do you have problems with tiredness? | 0.1077 | -0.0293 | -0.0761 | -0.0115 | 0.0020 | 0.1886 | -0.1145 | -0.2004 |
| 0.1559 | 0.7008 | 0.3170 | 0.8802 | 0.9788 | 0.0166\* | 0.2799 | 0.0676 |
| 2. Do you need to rest more? | -0.0477 | -0.0823 | -0.0907 | -0.0167 | 0.0143 | 0.2254 | 0.0471 | -0.0320 |
| 0.5311 | 0.2788 | 0.2327 | 0.8260 | 0.8515 | 0.0027\*\* | 0.6576 | 0.7724 |
| 3. Do you feel sleepy or drowsy? | 0.0705 | -0.0657 | 0.0572 | -0.0332 | 0.0044 | 0.0677 | -0.1806 | 0.0255 |
| 0.3539 | 0.3874 | 0.4524 | 0.6630 | 0.9545 | 0.3733 | 0.0867 | 0.8182 |
| 4. Do you have problems starting things? | 0.0255 | -0.0879 | -0.0438 | -0.0291 | 0.0660 | 0.1418 | -0.1114 | 0.1705 |
| 0.7376 | 0.2477 | 0.5653 | 0.7027 | 0.3857 | 0.0612 | 0.2932 | 0.1210 |
| 5. Do you lack energy? | 0.0105 | -0.0097 | -0.0977 | 0.0268 | 0.0088 | 0.1179 | -0.0261 | 0.0945 |
| 0.8903 | 0.8991 | 0.1984 | 0.7248 | 0.9080 | 0.1201 | 0.8059 | 0.3926 |
| 6. Do you have less strength in your muscles? | -0.0577 | -0.1033 | -0.1196 | 0.0616 | 0.0544 | -0.0331 | 0.1225 | -0.1049 |
| 0.4480 | 0.1736 | 0.1150 | 0.4185 | 0.4745 | 0.6641 | 0.2472 | 0.3423 |
| 7. Do you feel weak? | -0.0647 | -0.0676 | -0.1402 | 0.0884 | 0.0106 | 0.0017 | 0.1018 | -0.1408 |
| 0.3952 | 0.3740 | 0.0643 | 0.2445 | 0.8888 | 0.9825 | 0.3368 | 0.2014 |
| **Mental fatigue (total score)** | 0.0477 | -0.1410 | -0.0605 | -0.0327 | -0.0202 | 0.0430 | -0.0991 | -0.0939 |
| 0.5307 | 0.0628 | 0.4267 | 0.6674 | 0.7909 | 0.5717 | 0.3500 | 0.3955 |
| 8. Do you have difficulties concentrating? | 0.0585 | -0.1486 | -0.0864 | -0.0011 | -0.0147 | 0.1159 | -0.0483 | -0.1135 |
| 0.4423 | 0.0496\* | 0.2554 | 0.9888 | 0.8471 | 0.1267 | 0.6495 | 0.3040 |
| 9. Do you make slips of the tongue when speaking? | 0.1023 | -0.0467 | 0.1295 | -0.1501 | 0.0633 | 0.0004 | -0.1869 | -0.0054 |
| 0.1779 | 0.5393 | 0.0877 | 0.0474\* | 0.4056 | 0.9962 | 0.0760 | 0.9611 |
| 10. Do you find it more difficult to find the correct word? | -0.0066 | -0.0919 | -0.1238 | 0.0089 | 0.0149 | -0.0585 | -0.1504 | -0.1822 |
| 0.9314 | 0.2266 | 0.1025 | 0.9071 | 0.8449 | 0.4422 | 0.1548 | 0.0973 |
| 11. How is your memory? | -0.0185 | -0.0591 | -0.0437 | 0.0248 | -0.0794 | 0.0193 | 0.0436 | -0.1851 |
| 0.8085 | 0.4374 | 0.5655 | 0.7445 | 0.2962 | 0.8002 | 0.6817 | 0.0919 |

\*\**P* < 0.01; \**P* < 0.05.