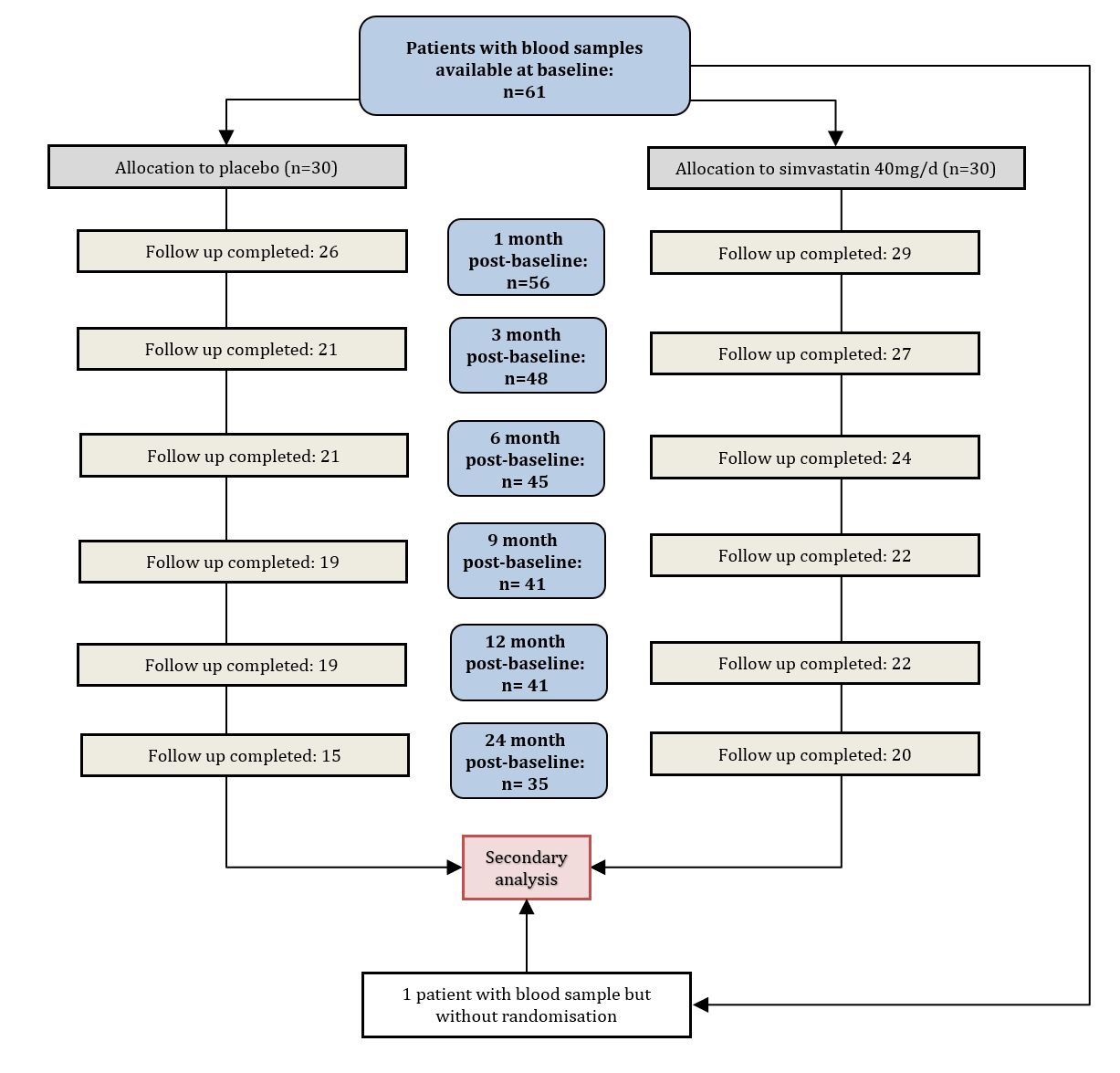
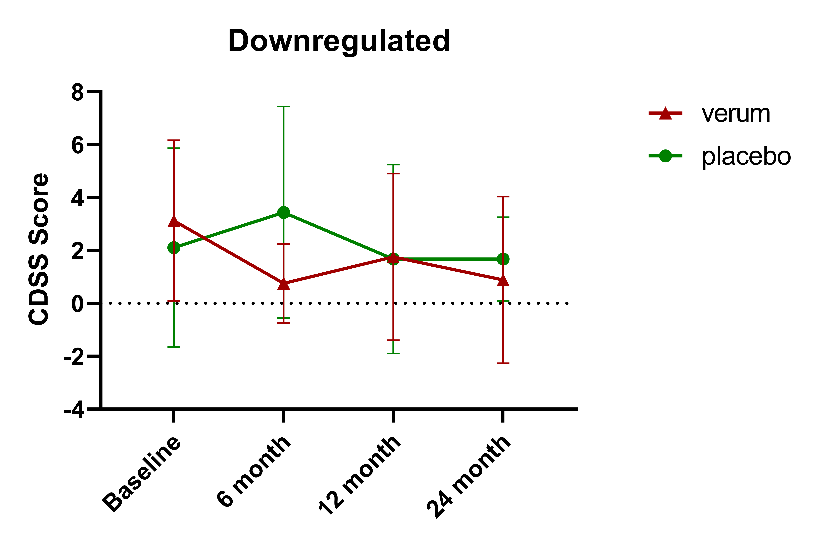
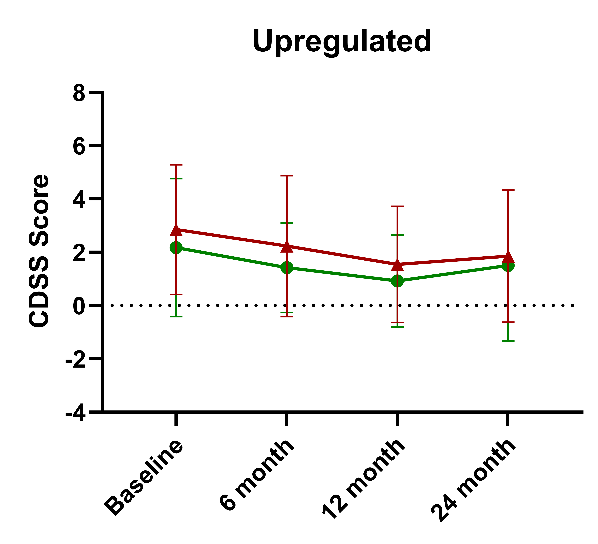
**Supplementary files**

**Supplementary Figure 1.** Flow Chart of the secondary analysis.



**Supplementary Figure 2.** CDSS total scores over time in the upregulated (**A**) and downregulated (**B**) group at baseline, 1, 6, 12, and 24 months follow up in the two treatment conditions: verum vs. placebo.



**B**

**A**

**Supplementary Table 1.** Gene expression in SSD (ddCT, e.g. compared to controls). sd=standard deviation, min=minimum, pctl.=percentile, max=maximum.

| **Gene** | **mean** | **sd** | **min** | **pctl. 25** | **pctl. 50** | **pctl. 75** | **max** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| n=61 |  |  |  |  |  |  |  |
| CCL7\_ddCT | -0.348 | 2.69 | -4.098 | -2.263 | -0.925 | 0.719 | 7.070 |
| STX1A\_ddCT | -0.326 | 1.652 | -2.259 | -1.483 | -0.784 | 0.176 | 4.777 |
| PTPN7\_ddCT | -0.167 | 0.737 | -1.802 | -0.659 | -0.255 | 0.244 | 2.225 |
| NAB2\_ddCT | -0.058 | 1.011 | -1.925 | -0.73 | -0.283 | 0.160 | 3.399 |
| CCL2\_ddCT | -0.409 | 1.571 | -4.104 | -1.538 | -0.418 | 0.526 | 3.192 |
| TNF\_ddCT | -0.713 | 1.404 | -2.896 | -1.318 | -0.963 | -0.617 | 5.092 |
| BAX\_ddCT | -0.16 | 1.871 | -2.422 | -1.391 | -0.979 | 1.109 | 4.808 |
| HMOX1\_ddCT | -0.994 | 2.114 | -2.579 | -1.881 | -1.728 | -1.480 | 7.517 |
| BCL10\_ddCT | -0.208 | 0.556 | -0.955 | -0.538 | -0.308 | 0.040 | 1.831 |
| CD163\_ddCT | 0.122 | 0.439 | -2.029 | -0.05 | 0.139 | 0.360 | 1.064 |
| IL1B\_ddCT | 0.409 | 1.898 | -2.744 | -1.042 | 0.338 | 1.612 | 4.839 |
| CCL20\_ddCT | 0.789 | 2.954 | -5.792 | -1.038 | 1.006 | 2.840 | 7.914 |
| CXCL2\_ddCT | 0.36 | 1.864 | -3.222 | -0.987 | 0.443 | 1.626 | 5.359 |
| IL6\_ddCT | 0.739 | 2.527 | -3.731 | -0.822 | 0.200 | 2.314 | 9.190 |
| MAFF\_ddCT | 0.379 | 1.505 | -3.462 | -0.542 | 0.478 | 1.433 | 2.983 |
| TNFAIP3\_ddCT | 0.688 | 1.323 | -1.176 | -0.424 | -0.004 | 1.998 | 3.144 |
| MXD1\_ddCT | -0.242 | 0.659 | -1.571 | -0.635 | -0.252 | 0.264 | 1.309 |
| SERPINB2\_ddCT | 0.044 | 1.254 | -2.667 | -0.735 | -0.31 | 0.782 | 3.734 |
| IL10\_ddCT | -0.146 | 1.299 | -3.418 | -0.870 | -0.096 | 0.602 | 2.816 |
| THBS1\_ddCT | 0.686 | 1.199 | -4.601 | 0.755 | 0.923 | 1.000 | 3.240 |
| ABCA1\_ddCT | 0.211 | 0.592 | -1.221 | -0.155 | 0.170 | 0.473 | 1.747 |
| ABCG1\_ddCT | 0.225 | 0.685 | -1.329 | -0.118 | 0.256 | 0.642 | 1.749 |
| MRC1\_ddCT | 0.418 | 0.698 | -1.541 | -0.074 | 0.363 | 0.934 | 2.154 |
| NR1H3\_ddCT | 0.083 | 0.458 | -1.989 | -0.134 | 0.085 | 0.299 | 1.169 |
| MVK\_ddCT | 0.145 | 0.380 | -1.716 | -0.012 | 0.214 | 0.409 | 0.934 |
| HGF\_ddCT | -0.011 | 0.448 | -2.174 | -0.244 | 0.002 | 0.286 | 0.939 |

**Supplementary Table 2.** Demographic data of patients receiving treatment as usual (TAU) and placebo or TAU and simvastatin. sd= standard deviation, BMI= Body Mass Index, PANSS= Positive and Negative Syndrome Scale, CDSS Calgary Depression Scale for Schizophrenia, Childhood Trauma was assessed with the Jeugd Trauma Vragenlijst (JVT)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **TAU+PLACEBO** | | | **TAU+SIMVASTATIN** | | |  |  |
| n=30 | | mean | sd | n=30 | mean | Sd | test statistic | p |
| BMI | | 24.00 | 3.72 |  | 24.00 | 4.15 | F=0.00 | 0.996 |
| Age baseline | | 27.70 | 7.76 |  | 25.17 | 4.45 | F=2.41 | 0.126 |
| Sex female n,(%) | | 8.00 | 27.00% |  | 8.00 | 27.00% | X2=0.00 | >0.999 |
| PANSS total | | 57.27 | 14.75 |  | 62.43 | 13.23 | F=2.04 | 0.159 |
| CDSS | | 2.83 | 3.70 |  | 3.57 | 3.88 | F=0.56 | 0.456 |
| Childhood Trauma | | 48.07 | 10.43 |  | 50.17 | 14.23 | F=0.43 | 0.517 |
| Illness duration (years) | | 1.27 | 1.01 |  | 1.37 | 1.10 | F=0.13 | 0.716 |

**Supplementary Table 3.** Patients’ medication categorised by the active ingredient group. SSRI=selective serotonin reuptake inhibitor, SSNRI=selective serotonin norepinephrine reuptake inhibitor.

|  |  |
| --- | --- |
|  | Number of patients |
| **Antipsychotics** | 53 |
| Olanzapine | 16 |
| Aripiprazole | 13 |
| Quetiapine | 9 |
| Clozapine | 6 |
| Haloperidol | 5 |
| Paliperidone | 4 |
| Risperidone | 3 |
| Amisulpride | 2 |
| Zuclopenthixol | 1 |
|  |  |
| **Antidepressants** | 11 |
| SSRI | 7 |
| SSNRI | 3 |
| Trycyclics | 1 |
|  |  |
| Benzodiazepines | 13 |
| Somatic medication | 28 |

**Supplementary Table 4.** Overview of the patients’ drug use. Hard drugs=amphetamines/ecstasy/cocaine/psilocybin/LSD/ketamine, soft drugs=cannabis.

|  |  |
| --- | --- |
|  | Number of patients |
| **Hard drugs** |  |
| Within the last month | 7 |
| Lifetime | 34 |
|  |  |
| **Soft drugs** |  |
| Within the last month | 15 |
| Lifetime | 50 |

**Supplementary Table 5.** Median gene expression per patient cluster. sd=standard deviation.

|  | **“Downregulated”** | | | | **“Upregulated”** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **N** | **Mean** | **SD** | **Median** | **N** | **Mean** | **SD** | **Median** |
| CCL7\_ddCT | 43 | -0.909 | 2.505 | -1.360 | 18 | 0.993 | 2.709 | 0.626 |
| STX1A\_ddCT | 43 | -0.468 | 1.668 | -0.849 | 18 | 0.011 | 1.609 | -0.484 |
| PTPN7\_ddCT | 43 | -0.207 | 0.700 | -0.339 | 18 | -0.070 | 0.83 | -0.167 |
| NAB2\_ddCT | 43 | -0.112 | 1.027 | -0.308 | 18 | 0.069 | 0.987 | 0.031 |
| CCL2\_ddCT | 43 | -0.713 | 1.476 | -0.677 | 18 | 0.315 | 1.594 | 0.421 |
| TNF\_ddCT | 43 | -0.876 | 1.425 | -1.055 | 18 | -0.323 | 1.308 | -0.841 |
| BAX\_ddCT | 43 | -0.486 | 1.693 | -1.182 | 18 | 0.617 | 2.089 | -0.714 |
| HMOX1\_ddCT | 43 | -0.980 | 2.115 | -1.751 | 18 | -1.026 | 2.173 | -1.710 |
| BCL10\_ddCT | 43 | -0.252 | 0.501 | -0.303 | 18 | -0.103 | 0.673 | -0.338 |
| CD163\_ddCT | 43 | 0.098 | 0.475 | 0.166 | 18 | 0.180 | 0.342 | 0.126 |
| IL1B\_ddCT | 43 | -0.571 | 1.185 | -0.500 | 18 | 2.750 | 1.006 | 2.766 |
| CCL20\_ddCT | 43 | -0.627 | 2.125 | -0.627 | 18 | 4.171 | 1.568 | 4.162 |
| CXCL2\_ddCT | 43 | -0.461 | 1.420 | -0.597 | 18 | 2.319 | 1.234 | 2.267 |
| IL6\_ddCT | 43 | -0.595 | 1.124 | -0.386 | 18 | 3.927 | 2.041 | 3.306 |
| MAFF\_ddCT | 43 | -0.138 | 1.409 | -0.066 | 18 | 1.615 | 0.893 | 1.659 |
| TNFAIP3\_ddCT | 43 | -0.038 | 0.742 | -0.12 | 18 | 2.422 | 0.545 | 2.578 |
| MXD1\_ddCT | 43 | -0.373 | 0.645 | -0.528 | 18 | 0.069 | 0.597 | 0.052 |
| SERPINB2\_ddCT | 43 | 0.069 | 1.245 | -0.310 | 18 | -0.018 | 1.311 | -0.301 |
| IL10\_ddCT | 43 | -0.117 | 1.286 | -0.227 | 18 | -0.216 | 1.364 | 0.231 |
| THBS1\_ddCT | 43 | 0.645 | 1.109 | 0.914 | 18 | 0.783 | 1.423 | 0.970 |
| ABCA1\_ddCT | 43 | 0.144 | 0.592 | 0.150 | 18 | 0.372 | 0.577 | 0.438 |
| ABCG1\_ddCT | 43 | 0.301 | 0.655 | 0.273 | 18 | 0.044 | 0.739 | 0.143 |
| MRC1\_ddCT | 43 | 0.403 | 0.759 | 0.268 | 18 | 0.452 | 0.540 | 0.512 |
| NR1H3\_ddCT | 43 | 0.112 | 0.520 | 0.158 | 18 | 0.015 | 0.255 | -0.031 |
| MVK\_ddCT | 43 | 0.163 | 0.412 | 0.226 | 18 | 0.100 | 0.294 | 0.098 |
| HGF\_ddCT | 43 | 0.038 | 0.479 | 0.026 | 18 | -0.129 | 0.347 | -0.095 |

**Supplementary Table 6.** Results of pairwise comparisons of PANSS total scores between the timepoints in the TAU+Placebo group. Df=degrees of freedom, SE=standard error, fu=follow up.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **“Down-regulated”** | | | | | **“Up-regulated”** | | | | |
| **Timepoint** | **estimate** | **SE** | **df** | **t.ratio** | **p.value** | **estimate** | **SE** | **df** | **t.ratio** | **p.value** |
|  |  |  |  |  |  |  |  |  |  |  |
| baseline - 1month | -2.55 | 2.92 | 252.00 | -0.88 | 0.574 | -2.64 | 4.67 | 260.00 | -0.56 | 0.807 |
| baseline - 3month | -3.57 | 3.14 | 260.00 | -1.14 | 0.491 | 2.51 | 4.92 | 266.00 | 0.51 | 0.807 |
| baseline - 6month | -1.74 | 3.14 | 261.00 | -0.56 | 0.773 | -0.32 | 4.92 | 266.00 | -0.07 | 0.995 |
| baseline - 9month | 3.31 | 3.21 | 263.00 | 1.03 | 0.531 | 3.87 | 5.23 | 269.00 | 0.74 | 0.087 |
| baseline - 12month | 4.81 | 3.21 | 263.00 | 1.50 | 0.329 | 3.87 | 5.23 | 269.00 | 0.74 | 0.087 |
| baseline - 24month | 3.13 | 3.48 | 266.00 | 0.90 | 0.574 | 6.79 | 5.65 | 271.00 | 1.20 | 0.087 |
| 1month - 3month | -1.01 | 3.20 | 255.00 | 0.31 | 0.832 | 5.15 | 5.15 | 253.00 | 1.00 | 0.087 |
| 1month - 6month | 0.82 | 3.20 | 256.00 | 0.26 | 0.839 | 2.31 | 5.15 | 253.00 | 0.45 | 0.087 |
| 1month - 9month | 5.87 | 3.27 | 258.00 | 1.80 | 0.258 | 6.51 | 5.44 | 257.00 | 1.20 | 0.087 |
| 1month - 12months | 7.37 | 3.27 | 258.00 | 2.25 | 0.258 | 6.51 | 5.44 | 257.00 | 1.20 | 0.087 |
| 1month - 24month | 5.68 | 3.53 | 261.00 | 1.61 | 0.327 | 9.43 | 5.85 | 261.00 | 1.61 | 0.087 |
| 3month - 6month | 1.82 | 3.37 | 250.00 | 0.54 | 0.773 | -2.83 | 5.31 | 246.00 | -0.53 | 0.087 |
| 3month - 9month | 6.88 | 3.43 | 252.00 | 2.00 | 0.258 | 1.36 | 5.60 | 251.00 | 0.24 | 0.893 |
| 3month - 12month | 8.38 | 3.43 | 252.00 | 2.44 | 0.258 | 1.36 | 5.60 | 251.00 | 0.24 | 0.893 |
| 3month - 24month | 6.69 | 3.69 | 257.00 | 1.81 | 0.258 | 4.28 | 5.99 | 255.00 | 0.71 | 0.087 |
| 6month - 9month | 5.05 | 3.42 | 248.00 | 1.48 | 0.329 | 4.20 | 5.60 | 251.00 | 0.75 | 0.087 |
| 6month - 12month | 6.55 | 3.42 | 248.00 | 1.92 | 0.258 | 4.20 | 5.60 | 251.00 | 0.75 | 0.087 |
| 6month - 24month | 4.87 | 3.68 | 253.00 | 1.32 | 0.392 | 7.11 | 5.99 | 255.00 | 1.87 | 0.087 |
| 9month - 12month | 1.50 | 3.47 | 246.00 | 0.43 | 0.777 | 0.00 | 5.81 | 246.00 | 0.00 | 1.000 |
| 9month - 24month | -0.19 | 3.72 | 251.00 | -0.05 | 0.960 | 2.92 | 6.20 | 251.00 | 0.47 | 0.087 |
| 12month - 24month | -1.69 | 3.27 | 251.00 | -0.45 | 0.777 | 2.92 | 6.20 | 251.00 | 0.47 | 0.087 |

**Supplementary Table 7.** Results of pairwise comparisons of PANSS total scores between the timepoints in the TAU+Simvastatin group. Df=degrees of freedom, SE=standard error, 12month=follow up.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **“Downregulated”** | | | | | **“Upregulated”** | | | | |
| **Timepoint** | **estimate** | **SE** | **df** | **t.ratio** | **p.value** | **estimate** | **SE** | **df** | **t.ratio** | **p.value** |
|  |  |  |  |  |  |  |  |  |  |  |
| baseline - 1month | 2.71 | 2.88 | 249.00 | 0.94 | 0.561 | -4.11 | 4.33 | 246.00 | -0.95 | 0.380 |
| baseline - 3month | 3.28 | 2.92 | 251.00 | 1.12 | 0.500 | -5.19 | 4.48 | 251.00 | -1.16 | 0.325 |
| baseline - 6month | 10.12 | 3.02 | 255.00 | 3.35 | 0.020 | 4.50 | 4.67 | 256.00 | 0.96 | 0.380 |
| baseline - 9month | 1.24 | 3.14 | 258.00 | 0.40 | 0.855 | 7.35 | 4.67 | 256.00 | 1.58 | 0.175 |
| baseline - 12month | 3.04 | 3.14 | 258.00 | 0.97 | 0.561 | 13.64 | 4.67 | 256.00 | 2.92 | 0.013 |
| baseline - 24month | 9.81 | 3.21 | 260.00 | 3.06 | 0.026 | 18.95 | 4.90 | 258.00 | 3.87 | 0.001 |
| 1month - 3month | 0.58 | 2.95 | 248.00 | 0.20 | 0.940 | -1.08 | 4.48 | 251.00 | -0.24 | 0.809 |
| 1month - 6month | 7.41 | 3.05 | 252.00 | 2.43 | 0.066 | 8.61 | 4.67 | 256.00 | 1.84 | 0.107 |
| 1month - 9month | -1.47 | 3.16 | 256.00 | -9.46 | 0.845 | 11.46 | 4.67 | 256.00 | 2.46 | 0.034 |
| 1month - 12month | 0.34 | 3.16 | 256.00 | 0.11 | 0.940 | 17.75 | 4.67 | 256.00 | 3.80 | 0.001 |
| 1month - 24month | 7.10 | 3.23 | 257.00 | 2.20 | 0.082 | 23.06 | 4.90 | 258.00 | 4.70 | <.0001 |
| 3month - 6month | 6.84 | 3.08 | 250.00 | 2.22 | 0.082 | 9.69 | 4.78 | 251.00 | 2.03 | 0.083 |
| 3month - 9month | -2.04 | 3.20 | 254.00 | -0.64 | 0.786 | 12.55 | 4.78 | 251.00 | 2.63 | 0.024 |
| 3month - 12month | -0.24 | 3.20 | 254.00 | -0.08 | 0.940 | 18.83 | 4.78 | 251.00 | 3.94 | 0.001 |
| 3month - 24month | 6.53 | 3.26 | 255.00 | 2.00 | 0.103 | 24.14 | 5.00 | 253.00 | 4.83 | <.0001 |
| 6month - 9month | -8.88 | 3.27 | 250.00 | -2.72 | 0.049 | 2.86 | 4.91 | 246.00 | 0.58 | 0.590 |
| 6month - 12month | -7.08 | 3.27 | 250.00 | -2.17 | 0.082 | 9.14 | 4.91 | 246.00 | 1.86 | 0.107 |
| 6month - 24month | -0.31 | 3.33 | 251.00 | -0.09 | 0.940 | 14.45 | 5.13 | 249.00 | 2.82 | 0.016 |
| 9month - 12month | 1.80 | 3.36 | 246.00 | 0.54 | 0.829 | 6.29 | 4.91 | 246.00 | 1.28 | 0.283 |
| 9month - 24month | 8.57 | 3.42 | 247.00 | 2.50 | 0.066 | 11.59 | 5.13 | 249.00 | 2.26 | 0.052 |
| 12month - 24month | 6.77 | 3.42 | 247.00 | 1.98 | 0.103 | 5.31 | 5.13 | 249.00 | 1.03 | 0.373 |