**Supplemental Digital Content 4, Supplementary Table 4**: Analysis results for Divided Attention Test: manual tracking variables (secondary endpoints; Completer Set, N = 42)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Furthest diagonal distance** | **RMS diagonal distance** | | **Percentage over the road** | | |
|  | **Emax** | **Emax** | **AUE0-8h** | **Emin** | **tEmin** | **AUE0-8h** |
|  | **Median  difference (p-value)** | **Median difference (p-value)** | **Median difference (p-value)** | **Median difference (p-value)** | **Median difference (p-value)** | **Median difference (p-value)** |
| **Overall treatment effect** | **0.0035** | **0.0130** | **0.0036** | **0.0005** | **0.0335** | **0.0002** |
| **HMO vs. PBO (Trial validity)** |  |  |  |  |  |  |
| HMO 8 mg - PBO | 5.5 (0.280) | 3.7 (0.441) | 16.7 (0.060) | -4.2 (0.117) | 0.0 (0.871) | -24.8 (0.060) |
| HMO 16 mg - PBO | **33.7 (0.044)** | **9.7 (0.004)** | **39.5 (0.003)** | **-8.4 (<0.001)** | -1.0 (0.154) | **-48.1 (0.003)** |
| **Cebranopadol vs. PBO** |  |  |  |  |  |  |
| Cebranopadol 200 µg - PBO | 1.5 (0.878) | 0.1 (>.999) | 4.1 (0.644) | -1.5 (0.280) | 0.0 (>0.999) | -10.4 (0.088) |
| Cebranopadol 400 µg - PBO | 4.7 (0.644) | 2.9 (0.164) | 19.1 (0.164) | -4.0 (0.164) | -0.5 (0.337) | -27.5 (0.280) |
| Cebranopadol 800 µg - PBO | 31.4 (0.164) | 8.7 (0.060) | **21.1 (0.044)** | **-8.5 (0.004)** | 1.5 (0.121) | **-31.6 (0.003**) |
| **Cebranopadol vs. HMO** |  |  |  |  |  |  |
| Cebranopadol 200 µg - HMO 8 mg | 6.4 (0.878) | -0.3 (0.878) | -4.2 (0.533) | 0.4 (>.999) | 0.0 (0.211) | 3.1 (0.533) |
| Cebranopadol 400 µg - HMO 8 mg | 8.7 (0.441) | 0.7 (0.755) | 0.0 (>.999) | -0.9 (0.878) | 0.0 (>0.999) | -5.0 (0.755) |
| Cebranopadol 800 µg - HMO 8 mg | **28.0 (0.008)** | **4.9 (0.044)** | 12.9 (0.117) | **-5.4 (0.028)** | 2.5 (0.081) | **-19.6 (0.028)** |
| Cebranopadol 200 µg - HMO 16 mg | **-22.2 (0.044)** | -9.0 (0.088) | **-30.7 (0.044)** | **5.0 (0.020)** | 1.5 (0.117) | **33.2 (0.044)** |
| Cebranopadol 400 µg - HMO 16 mg | -31.0 (0.088) | -5.0 (0.349) | -23.0 (0.280) | 3.4 (0.211) | 0.0 (0.871) | **28.0 (0.020)** |
| Cebranopadol 800 µg - HMO 16 mg | -14.9 (0.280) | -1.3 (0.644) | -20.0 (0.164) | 3.5 (0.441) | **2.5 (0.003)** | 30.8 (0.280) |

Overall treatment effect was assessed using Friedman’s test. Pairwise comparisons were assessed using the sign test. Bold p-values indicate statistically significant differences.  
AUE0-xh = area under the curve from time zero to x hours post-dose; Emax = maximum effect; Emin = minimum effect; HMO = hydromorphone immediate release; N = number of subjects; PBO = placebo (fully randomized only); RMS = root mean square; tEmin = time to minimum effect.