**Supplemental Digital Content 2, Supplementary Table 2:** Selected secondary endpoints (VAS and ARCI assessments) – nonparametric analysis; p-values of pharmacodynamics results

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **HMO vs. PBO** | **Cebranopadol vs. PBO** | **Cebranopadol vs. HMO** |
| 8 mg - PBO | 16 mg - PBO | 200 µg - PBO | 400 µg - PBO | 800 µg - PBO | 200 µg - 8 mg | 400 µg - 8 mg | 800 µg - 8 mg | 200 µg - 16 mg | 400 µg - 16 mg | 800 µg - 16 mg |
| **Overall Effects** |
| Overall Drug Liking VAS (Emax) | **<.001 (+)** | **<.001 (+)** | 0.690 | 0.076 | **0.006 (+)** | **0.001 (-)** | **0.017 (-)** | 0.143 | **<.001 (-)** | **<.001 (-)** | **<.001 (-)** |
| Take Drug Again VAS (Emax) | **<.001 (+)** | **<.001 (+)** | 0.248 | **0.011 (+)** | **<0.001 (+)** | **<0.001 (-)** | 0.065 | 0.296 | **<.001 (-)** | **<.001 (-)** | **<.001 (-)** |
| **Positive Effects** |
| Good Effects VAS (Emax) | **<.001 (+)** | **<.001 (+)** | 0.711 | 0.678 | **<.001 (+)** | **0.003 (-)** | **0.020 (-)** | 0.608 | **<.001 (-)** | **<.001 (-)** | **<.001 (-)** |
| High VAS (Emax) | **<.001 (+)** | **<.001 (+)** | 0.857 | 0.495 | **<.001 (+)** | **<.001 (-)** | **<.001 (-)** | 0.399 | **<.001 (-)** | **<.001 (-)** | **<.001 (-)** |
| ARCI MBG (Emax) | **0.006 (+)** | **<.001 (+)** | 0.851 | 0.327 | **<.001 (+)** | **0.016 (-)** | 0.473 | 0.150 | **<.001 (-)** | **<.001 (-)** | 0.121 |
| **Negative Effects** |
| Bad Effects VAS (Emax) | 0.383 | **0.003 (+)** | >.999 | 0.804 | **0.004 (+)** | 0.648 | 0.503 | 0.327 | 0.052 | 0.108 | >.999 |
| Feeling Sick VAS (Emax) | 0.832 | **0.009 (+)** | >.999 | >.999 | 0.345 | >.999 | >.999 | 0.327 | 0.215 | **0.016 (-)** | 0.458 |
| **Sedative Effects** |
| Alertness/Drowsiness VAS (Emin) | **<.001 (-)** | **<.001 (-)** | 0.327 | **0.013 (-)** | **<.001 (-)** | **0.016 (+)** | 0.362 | >.999 | **0.006 (+)** | **<.001 (+)** | 0.377 |
| ARCI PCAG (Emax) | **<.001 (+)** | **<.001 (+)** | 0.829 | 0.178 | **<.001 (+)** | **0.004 (-)** | 0.054 | 0.218 | **<.001 (-)** | **<.001 (-)** | **0.047 (-)** |
| **Other Effects** |
| Any Effect VAS (Emax) | **0.002 (+)** | **<.001 (+)** | 0.856 | 0.108 | **<.001 (+)** | **0.001 (-)** | 0.200 | 0.856 | **<.001 (-)** | **<.001 (-)** | **0.002 (-)** |

Bold p-values indicate statistically significant differences. The symbols (+) and (–) show the direction, i.e., whether the difference was positive or negative.

ARCI = Addiction Research Center Inventory; Emax = maximum effect Emin = minimum effect; HMO = hydromorphone immediate release; MBG = morphine-benzedrine group; PBO = placebo (fully randomized only); PCAG = pentobarbital-chlorpromazine-alcohol group; VAS = visual analogue scale..