

Table S1: Summary of Concomitant Medications

| Characteristic | Statistic | 10-0011 | 11-0020 | 12-0005 | 13-0001 | 13-0006 | Overall |
|-------------------------|-----------|------------|------------|-------------|-------------|------------|--------------|
| Methocarbamol: No Use | N (%) | 1 (8.33%) | 7 (14.6%) | 44 (36.1%) | 855 (98.7%) | 43 (65.2%) | 950 (85.3%) |
| Methocarbamol: Use | N (%) | 11 (91.7%) | 41 (85.4%) | 78 (63.9%) | 11 (1.27%) | 23 (34.8%) | 164 (14.7%) |
| Clonidine: No Use | N (%) | 0 (0%) | 7 (14.6%) | 52 (42.6%) | 842 (97.2%) | 66 (100%) | 967 (86.8%) |
| Clonidine: Use | N (%) | 12 (100%) | 41 (85.4%) | 70 (57.4%) | 24 (2.77%) | 0 (0%) | 147 (13.2%) |
| Hydroxyzine: No Use | N (%) | 0 (0%) | 3 (6.25%) | 35 (28.7%) | 811 (93.6%) | 32 (48.5%) | 881 (79.1%) |
| Hydroxyzine: Use | N (%) | 12 (100%) | 45 (93.8%) | 87 (71.3%) | 55 (6.35%) | 34 (51.5%) | 233 (20.9%) |
| Oxycodone: No Use | N (%) | 5 (41.7%) | 14 (29.2%) | 68 (55.7%) | 706 (81.5%) | 49 (74.2%) | 842 (75.6%) |
| Oxycodone: Use | N (%) | 7 (58.3%) | 34 (70.8%) | 54 (44.3%) | 160 (18.5%) | 17 (25.8%) | 272 (24.4%) |
| Cocaine: No Use | N (%) | 10 (83.3%) | 31 (64.6%) | 95 (77.9%) | 484 (55.9%) | 39 (59.1%) | 659 (59.2%) |
| Cocaine: Use | N (%) | 2 (16.7%) | 17 (35.4%) | 27 (22.1%) | 382 (44.1%) | 27 (40.9%) | 455 (40.8%) |
| Amphetamine: No Use | N (%) | 12 (100%) | 31 (64.6%) | 101 (82.8%) | 671 (77.5%) | 43 (65.2%) | 858 (77.0%) |
| Amphetamine: Use | N (%) | 0 (0%) | 17 (35.4%) | 21 (17.2%) | 195 (22.5%) | 23 (34.8%) | 256 (23.0%) |
| Methadone: No Use | N (%) | 4 (33.3%) | 19 (39.6%) | 117 (95.9%) | 757 (87.4%) | 64 (97.0%) | 961 (86.3%) |
| Methadone: Use | N (%) | 8 (66.7%) | 29 (60.4%) | 5 (4.10%) | 109 (12.6%) | 2 (3.03%) | 153 (13.7%) |
| Cannabinoid: No Use | N (%) | 10 (83.3%) | 14 (29.2%) | 48 (39.3%) | 511 (59.0%) | 30 (45.5%) | 613 (55.0%) |
| Cannabinoid: Use | N (%) | 2 (16.7%) | 34 (70.8%) | 74 (60.7%) | 355 (41.0%) | 36 (54.5%) | 501 (45.0%) |
| Barbiturate: No Use | N (%) | 12 (100%) | 45 (93.8%) | 122 (100%) | 842 (97.2%) | 65 (98.5%) | 1086 (97.5%) |
| Barbiturate: Use | N (%) | 0 (0%) | 3 (6.25%) | 0 (0%) | 24 (2.77%) | 1 (1.52%) | 28 (2.51%) |
| Methamphetamine: No Use | N (%) | 4 (33.3%) | 20 (41.7%) | 110 (90.2%) | 781 (90.2%) | 58 (87.9%) | 973 (87.3%) |
| Methamphetamine: Use | N (%) | 8 (66.7%) | 28 (58.3%) | 12 (9.84%) | 85 (9.82%) | 8 (12.1%) | 141 (12.7%) |
| Phencyclidine: No Use | N (%) | 12 (100%) | 46 (95.8%) | 114 (93.4%) | 832 (96.1%) | 66 (100%) | 1070 (96.1%) |
| Phencyclidine: Use | N (%) | 0 (0%) | 2 (4.17%) | 8 (6.56%) | 34 (3.93%) | 0 (0%) | 44 (3.95%) |
| Codeine: No Use | N (%) | 12 (100%) | 47 (97.9%) | 120 (98.4%) | 351 (40.5%) | 66 (100%) | 596 (53.5%) |
| Codeine: Use | N (%) | 0 (0%) | 1 (2.08%) | 2 (1.64%) | 515 (59.5%) | 0 (0%) | 518 (46.5%) |
| Hydrocodone: No Use | N (%) | 12 (100%) | 25 (52.1%) | 104 (85.2%) | 735 (84.9%) | 65 (98.5%) | 941 (84.5%) |
| Hydrocodone: Use | N (%) | 0 (0%) | 23 (47.9%) | 18 (14.8%) | 131 (15.1%) | 1 (1.52%) | 173 (15.5%) |
| Hydromorphone: No Use | N (%) | 0 (0%) | 42 (87.5%) | 117 (95.9%) | 327 (37.8%) | 66 (100%) | 552 (49.6%) |
| Hydromorphone: Use | N (%) | 12 (100%) | 6 (12.5%) | 5 (4.10%) | 539 (62.2%) | 0 (0%) | 562 (50.4%) |
| Morphine: No Use | N (%) | 12 (100%) | 42 (87.5%) | 116 (95.1%) | 279 (32.2%) | 66 (100%) | 515 (46.2%) |
| Morphine: Use | N (%) | 0 (0%) | 6 (12.5%) | 6 (4.92%) | 587 (67.8%) | 0 (0%) | 599 (53.8%) |
| Oxymorphone: No Use | N (%) | 12 (100%) | 47 (97.9%) | 120 (98.4%) | 721 (83.3%) | 66 (100%) | 966 (86.7%) |
| Oxymorphone: Use | N (%) | 0 (0%) | 1 (2.08%) | 2 (1.64%) | 145 (16.7%) | 0 (0%) | 148 (13.3%) |
| Heroin: No Use | N (%) | 12 (100%) | 26 (54.2%) | 33 (27.0%) | 866 (100%) | 66 (100%) | 1003 (90.0%) |
| Heroin: Use | N (%) | 0 (0%) | 22 (45.8%) | 89 (73.0%) | 0 (0%) | 0 (0%) | 111 (9.96%) |

Use = subject received the concomitant medication at any point during the study, No Use = subject did not receive the concomitant medication at any point during the study

Table S2: Results from Sensitivity Analysis Evaluating the Effect of Adding IIV onto Alpha, Using the Phase 3 Data Alone, and Eliminating the Effect of Age on QTcAbs

| | Final Model | | Adding IIV on Alpha | | Phase 3 data Only | | Eliminating Age | |
|--|-------------|-------|---------------------|-------|-------------------|-------|-----------------|-------|
| | Estimate | %RSE | Estimate | %RSE | Estimate | %RSE | Estimate | %RSE |
| QTcAbs (msec) | 400 | 0.2 | 400 | 0.229 | 400 | 0.1 | 411 | 0.2 |
| Alpha | 0.333 | | 0.333 | | 0.333 | | 0.333 | |
| Sex on QTcAbs | 0.0189 | 13.7 | 0.0196 | 13.7 | 0.018 | 17.1 | 0.0164 | 16.3 |
| COWS on alpha | 0.00151 | 52.1 | 0.00157 | 43.2 | 0.00312 | 24.8 | 0.0016 | 49.5 |
| Hydroxyzine on QTcAbs | 0.00423 | 35.7 | 0.00473 | 31.3 | 0.0079 | 34.1 | 0.00398 | 37.4 |
| Methadone on QTcAbs | 0.0153 | 18.4 | 0.0156 | 18.2 | 0.00293 | 76.1 | 0.0148 | 18.4 |
| Age on QTcAbs | 0.324 | 7 | 0.326 | 7.2 | 0.334 | 4.1 | | |
| Holter vs non-Holter on QTcAbs | -0.00423 | 24.6 | -0.00314 | 31.5 | -0.00426 | 24.4 | -0.00409 | 24.7 |
| Central vs non-central reading on QTcAbs | -0.021 | 11.5 | -0.0195 | 13.5 | -0.021 | | -0.0166 | 16.3 |
| Concentration-related slope (msec/ng/mL) | -0.0507 | 168.8 | -0.0604 | 131 | -0.0157 | 595.5 | -0.0431 | 200.9 |
| Codeine on QTcAbs | 0.00327 | 35.2 | 0.00318 | 34.3 | 0.00382 | 30.1 | 0.00326 | 34.4 |
| Oxycodone on QTcAbs | -0.00378 | 43.4 | -0.00332 | 47.0 | -0.00205 | 104.9 | -0.00392 | 40.8 |
| Phencyclidine on QTcAbs | 0.00861 | 44.1 | 0.00958 | 40.6 | 0.0109 | 40.9 | 0.00844 | 43.6 |
| Barbiturates on QTcAbs | 0.0124 | 38.9 | 0.0116 | 42.2 | 0.0135 | 35 | 0.0119 | 39.3 |
| Cocaine on QTcAbs | 0.00428 | 28 | 0.00429 | 28.4 | 0.00322 | 40.1 | 0.00438 | 26.7 |
| IIV on QTcAbs (±msec) | 14.3 | 5.2 | 14.4 | 5.3 | 14.8 | 6.1 | 14.7 | 5.2 |
| IIV on concentration-related slope (±msec/ng/mL) | 0.767 | 33.1 | 0.581 | 38.9 | 0.7714 | 30.1 | 0.7609 | 35.8 |
| IIV on alpha | NA | | 0.0535 | 14.7 | NA | | NA | |
| Residual error (±msec) | 10.6 | 3.3 | 10.2 | 3.17 | 10.3 | 2.6 | 10.6 | 3.3 |