**Supplemental Information**

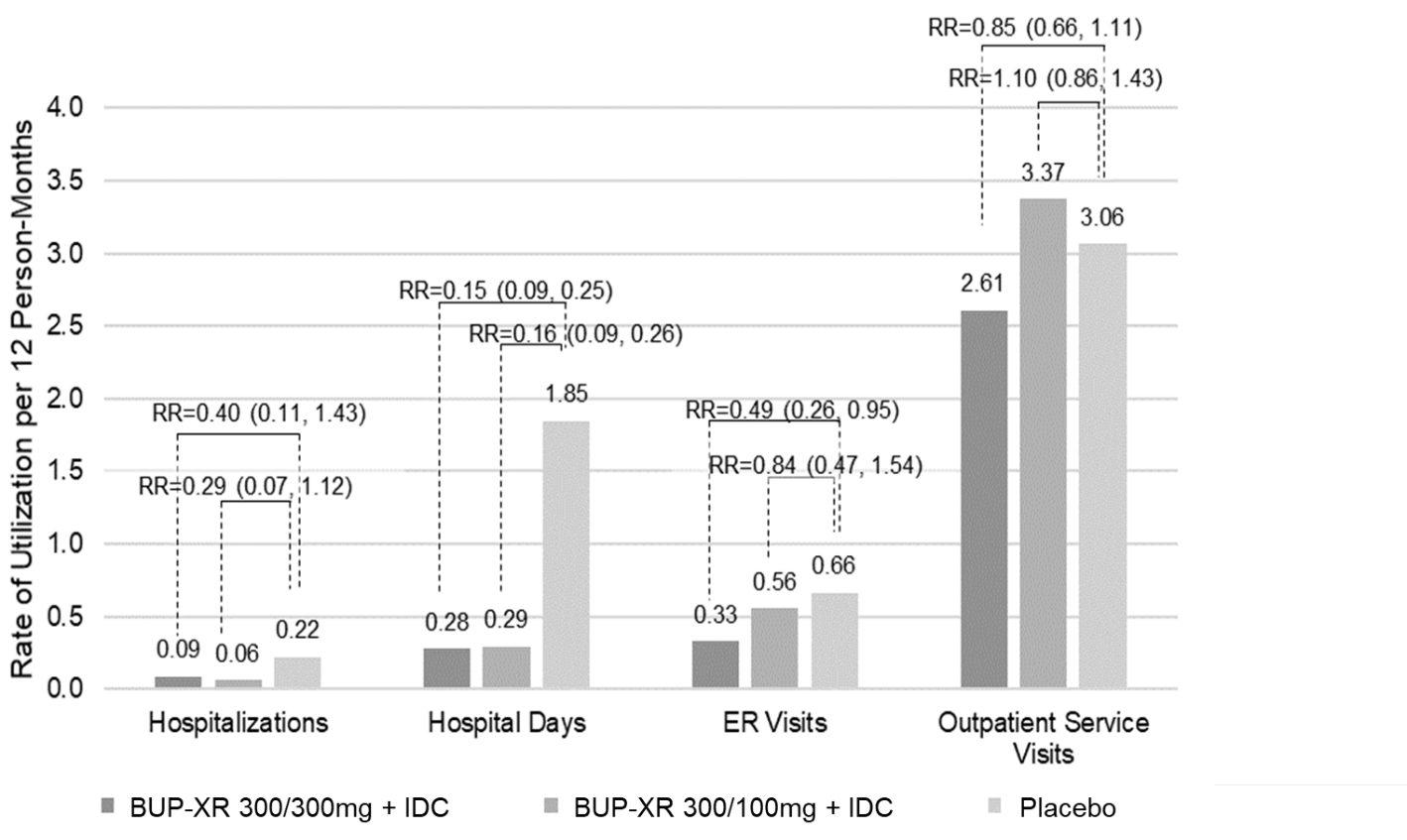
Supplemental Table 1. Patient-centered Outcomes at Screening at All Time Pointsa

| **Measure** | **Time point** | **BUP-XR 300/300mg** | | **BUP-XR 300/100mg** | | **Placebo** | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **N** | **Statistic** | **N** | **Statistic** | **N** | **Statistic** |
| EQ-5D-5L Index, Mean (SD) | Screening | 194 | 0.794 (0.175) | 194 | 0.773 (0.177) | 99 | 0.800 (0.159) |
| Week 1/ Baseline | 193 | 0.890 (0.119) | 192 | 0.901 (0.116) | 97 | 0.904 (0.119) |
| Week 9 | 155 | 0.924 (0.106) | 156 | 0.926 (0.108) | 49 | 0.893 (0.120) |
| Week 21 | 130 | 0.931 (0.110) | 131 | 0.919 (0.108) | 35 | 0.887 (0.140) |
| Week 25/ End of Study | 130 | 0.921 (0.124) | 126 | 0.905 (0.118) | 39 | 0.859 (0.149) |
| EQ-5D-5L VAS, Mean (SD) | Screening | 194 | 66.7 (19.7) | 194 | 65.6 (20.9) | 99 | 66.0 (21.7) |
| Week 1/ Baseline | 193 | 78.7 (15.8) | 192 | 77.8 (17.7) | 97 | 78.2 (14.2) |
| Week 9 | 155 | 79.2 (17.1) | 156 | 80.2 (16.1) | 49 | 72.0 (20.1) |
| Week 21 | 130 | 80.9 (17.1) | 131 | 82.5 (15.3) | 35 | 73.9 (16.0) |
| Week 25/ End of Study | 130 | 80.9 (15.7) | 126 | 82.7 (13.8) | 39 | 73.4 (14.1) |
| SF-36v2 PCS, Mean (SD) | Screening | 194 | 47.7 (8.9) | 194 | 47.3 (9.0) | 99 | 49.2 (9.3) |
| Week 1/ Baseline | 192 | 52.2 (7.4) | 191 | 51.5 (8.0) | 97 | 53.0 (7.8) |
| Week 9 | 155 | 53.8 (6.9) | 156 | 53.5 (7.7) | 49 | 52.2 (8.5) |
| Week 21 | 130 | 54.5 (6.6) | 131 | 53.8 (7.4) | 35 | 51.3 (9.5) |
| Week 25/ End of Study | 130 | 54.2 (6.4) | 126 | 53.6 (7.3) | 39 | 51.1 (8.5) |
| SF-36v2 MCS, Mean (SD) | Screening | 194 | 43.0 (11.9) | 194 | 41.6 (12.0) | 99 | 40.7 (11.1) |
| Week 1/ Baseline | 192 | 48.2 (9.2) | 191 | 47.5 (9.2) | 97 | 44.9 (9.6) |
| Week 9 | 155 | 53.6 (7.5) | 156 | 52.6 (6.7) | 49 | 48.1 (10.8) |
| Week 21 | 130 | 52.6 (8.4) | 131 | 52.6 (8.2) | 35 | 45.8 (11.7) |
| Week 25/ End of Study | 130 | 52.6 (8.7) | 126 | 52.3 (8.3) | 39 | 46.8 (10.2) |
| SF-36v2 Physical functioning, Mean (SD) | Screening | 194 | 77.3 (24.5) | 194 | 76.6 (24.6) | 99 | 79.0 (25.5) |
| Week 1/ Baseline | 192 | 88.4 (18.8) | 191 | 85.7 (20.9) | 97 | 89.0 (18.2) |
| Week 9 | 155 | 89.7 (20.2) | 156 | 88.9 (20.1) | 49 | 86.2 (21.5) |
| Week 21 | 130 | 90.8 (17.2) | 131 | 88.1 (23.2) | 35 | 86.0 (24.2) |
| Week 25/ End of Study | 130 | 92.5 (15.3) | 126 | 88.5 (22.6) | 39 | 86.8 (20.7) |
| SF-36v2 Role physical, Mean (SD) | Screening | 194 | 68.2 (27.3) | 194 | 66.1 (26.0) | 99 | 72.5 (28.3) |
| Week 1/ Baseline | 192 | 82.5 (21.0) | 191 | 78.9 (23.8) | 97 | 81.8 (21.8) |
| Week 9 | 155 | 90.9 (18.5) | 156 | 87.9 (19.7) | 49 | 82.7 (26.6) |
| Week 21 | 130 | 90.0 (18.3) | 131 | 86.3 (24.0) | 35 | 77.3 (30.0) |
| Week 25/ End of Study | 130 | 88.6 (18.9) | 126 | 86.3 (21.0) | 39 | 77.6 (25.3) |
| SF-36v2 Bodily pain, Mean (SD) | Screening | 194 | 57.1 (27.5) | 194 | 54.8 (26.5) | 99 | 58.4 (27.3) |
| Baseline | 192 | 69.0 (22.4) | 191 | 69.3 (23.8) | 97 | 67.6 (24.7) |
| Week 9 | 155 | 81.0 (20.9) | 156 | 81.1 (21.2) | 49 | 73.7 (25.5) |
| Week 21 | 130 | 81.6 (20.7) | 131 | 81.1 (21.2) | 35 | 69.7 (24.9) |
| Week 25/ End of Study | 130 | 79.3 (21.5) | 126 | 79.4 (20.3) | 39 | 71.9 (23.8) |
| SF-36v2 General health, Mean (SD) | Screening | 194 | 58.2 (20.0) | 194 | 55.7 (22.7) | 99 | 57.5 (21.4) |
| Week 1/ Baseline | 192 | 68.9 (18.7) | 191 | 67.6 (19.8) | 97 | 67.7 (18.8) |
| Week 9 | 155 | 73.9 (17.8) | 156 | 71.5 (20.3) | 49 | 65.4 (20.6) |
| Week 21 | 130 | 75.5 (17.8) | 131 | 75.5 (19.7) | 35 | 62.3 (20.0) |
| Week 25/ End of Study | 130 | 74.4 (18.2) | 126 | 74.8 (18.6) | 39 | 59.9 (18.2) |
| SF-36v2 Vitality, Mean (SD) | Screening | 194 | 45.8 (20.5) | 194 | 43.9 (19.7) | 99 | 43.1 (19.8) |
| Week 1/ Baseline | 192 | 57.3 (17.7) | 191 | 55.6 (19.7) | 97 | 53.4 (18.7) |
| Week 9 | 155 | 66.8 (18.2) | 156 | 64.7 (18.0) | 49 | 59.2 (18.7) |
| Week 21 | 130 | 66.8 (19.0) | 131 | 67.6 (17.8) | 35 | 54.8 (21.2) |
| Week 25/ End of Study | 130 | 67.5 (18.9) | 126 | 67.0 (18.6) | 39 | 53.8 (17.6) |
| SF-36v2 Social functioning, Mean (SD) | Screening | 194 | 64.2 (28.4) | 194 | 61.0 (28.4) | 99 | 61.2 (27.8) |
| Week 1/ Baseline | 192 | 79.5 (21.6) | 191 | 76.0 (24.2) | 97 | 75.4 (23.7) |
| Week 9 | 155 | 89.6 (17.4) | 156 | 90.1 (16.7) | 49 | 78.8 (25.2) |
| Week 21 | 130 | 88.0 (19.1) | 131 | 88.7 (18.0) | 35 | 71.8 (26.5) |
| Week 25/ End of Study | 130 | 88.5 (18.3) | 126 | 86.6 (20.9) | 39 | 76.0 (25.2) |
| SF-36v2 Role emotional, Mean (SD) | Screening | 194 | 74.6 (26.9) | 194 | 72.0 (27.2) | 99 | 72.8 (27.8) |
| Week 1/ Baseline | 192 | 85.6 (19.6) | 191 | 85.6 (19.8) | 97 | 81.1 (21.2) |
| Week 9 | 155 | 93.5 (16.2) | 156 | 91.8 (15.7) | 49 | 84.4 (26.1) |
| Week 21 | 130 | 91.9 (16.3) | 131 | 88.6 (22.7) | 35 | 79.0 (27.6) |
| Week 25/ End of Study | 130 | 91.3 (17.2) | 126 | 90.1 (18.3) | 39 | 81.2 (23.8) |
| SF-36v2 Mental health, Mean (SD) | Screening | 194 | 60.6 (22.1) | 194 | 57.9 (22.4) | 99 | 56.5 (20.4) |
| Week 1/ Baseline | 192 | 70.1 (17.3) | 191 | 68.0 (17.7) | 97 | 63.4 (17.9) |
| Week 9 | 155 | 81.0 (15.4) | 156 | 78.3 (14.7) | 49 | 69.9 (19.2) |
| Week 21 | 130 | 79.2 (17.0) | 131 | 79.2 (16.0) | 35 | 67.6 (21.5) |
| Week 25/ End of Study | 130 | 79.2 (17.4) | 126 | 78.1 (17.4) | 39 | 69.2 (17.9) |
| Participants employed (full-time or part-time), N (%) | Screening | 194 | 79.0 (40.7) | 194 | 63.0 (32.5) | 99 | 41.0 (41.4) |
| Week 1/ Baseline | 195 | 78.0 (40.0) | 193 | 65.0 (33.7) | 98 | 45.0 (45.9) |
| Week 9 | 155 | 74.0 (47.7) | 156 | 60.0 (38.5) | 49 | 19.0 (38.8) |
| Week 21 | 130 | 57.0 (43.8) | 131 | 55.0 (42.0) | 35 | 12.0 (34.3) |
| Week 25/ End of Study | 130 | 66.0 (50.8) | 126 | 55.0 (43.7) | 39 | 13.0 (33.3) |
| Hours worked per week, Mean (SD) | Screening | 194 | 14.0 (19.4) | 194 | 10.8 (17.5) | 99 | 14.0 (18.5) |
| Week 1/ Baseline | 195 | 14.2 (19.5) | 193 | 11.1 (17.9) | 98 | 14.8 (19.0) |
| Week 9 | 155 | 17.2 (20.6) | 156 | 13.6 (19.2) | 49 | 13.9 (19.5) |
| Week 21 | 130 | 16.7 (20.7) | 131 | 15.1 (20.1) | 35 | 11.0 (17.6) |
| Week 25/ End of Study | 130 | 17.7 (20.7) | 126 | 15.6 (20.0) | 39 | 11.6 (17.0) |
| Participants Uninsured, N (%) | Screening | 194 | 79.0 (40.7) | 194 | 79.0 (40.7) | 99 | 39.0 (39.4) |
| Week 1/ Baseline | 195 | 86.0 (44.1) | 193 | 78.0 (40.4) | 98 | 37.0 (37.8) |
| Week 9 | 155 | 66.0 (42.6) | 156 | 64.0 (41.0) | 49 | 18.0 (36.7) |
| Week 21 | 130 | 52.0 (40.0) | 131 | 47.0 (35.9) | 35 | 17.0 (48.6) |
| Week 25/ End of Study | 130 | 52.0 (40.0) | 126 | 45.0 (35.7) | 39 | 18.0 (46.2) |

Supplemental Table 2. Change from Baseline in EQ-5D and SF-36v2 Scores at Week 25 based on MMRM Adjusting for Age and Race

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Measure | Placebo | | BUP-XR 300/100mg | | Difference between BUP-XR 300/100mg and Placebo | | BUP-XR 300/300mg | | Difference between BUP-XR 300/300mg and Placebo | |
|  | LS mean (SE) | p-value | LS mean (SE) | p-value | LS mean difference (SE) | p-value | LS mean (SE) | p-value | LS mean difference (SE) | p-value |
|  | Change from Baseline to Week 25 | | | | | | | | | |
| EQ-5D |  |  |  |  |  |  |  |  |  |  |
| Index | -0.05 (0.02) | 0.009 | -0.01 (0.01) | 0.356 | 0.04 (0.02) | 0.056 | 0.01 (0.01) | 0.378 | 0.06 (0.02) | 0.003 |
| VAS | -2.6 (2.2) | 0.235 | 4.9 (1.2) | <0.001 | 7.4 (2.5) | 0.003 | 3.1 (1.2) | 0.010 | 5.7 (2.5) | 0.021 |
| SF-36v2 |  |  |  |  |  |  |  |  |  |  |
| Physical component summary | -1.5 (0.9) | 0.100 | 1.5 (0.5) | 0.005 | 3.0 (1.0) | 0.003 | 2.1 (0.5) | <0.001 | 3.6 (1.0) | <0.001 |
| Mental component summary | 1.9 (1.3) | 0.131 | 4.2 (0.7) | <0.001 | 2.3 (1.4) | 0.107 | 4.6 (0.7) | <0.001 | 2.7 (1.4) | 0.057 |
| Physical functioning | -2.1 (2.3) | 0.355 | 0.3 (1.3) | 0.838 | 2.4 (2.5) | 0.342 | 3.1 (1.3) | 0.022 | 5.3 (2.5) | 0.036 |
| Role physical | 0.1 (2.9) | 0.972 | 5.4 (1.7) | 0.001 | 5.3 (3.3) | 0.108 | 7.0 (1.7) | <0.001 | 6.9 (3.3) | 0.037 |
| Bodily pain | 1.8 (3.3) | 0.592 | 8.0 (2.1) | <0.001 | 6.2 (3.5) | 0.078 | 8.5 (2.1) | <0.001 | 6.7 (3.5) | 0.053 |
| General health | -6.0 (2.6) | 0.022 | 6.1 (1.5) | <0.001 | 12.0 (2.9) | <0.001 | 6.2 (1.5) | <0.001 | 12.2 (2.9) | <0.001 |
| Vitality | 0.9 (2.8) | 0.752 | 11.2 (1.7) | <0.001 | 10.3 (3.1) | <0.001 | 11.4 (1.7) | <0.001 | 10.5 (3.0) | <0.001 |
| Social functioning | 2.9 (3.3) | 0.379 | 8.4 (1.9) | <0.001 | 5.5 (3.5) | 0.117 | 10.2 (2.0) | <0.001 | 7.4 (3.5) | 0.037 |
| Role emotional | 1.8 (2.7) | 0.511 | 3.4 (1.5) | 0.025 | 1.6 (3.1) | 0.606 | 5.3 (1.5) | <0.001 | 3.6 (3.1) | 0.245 |
| Mental health | 4.6 (2.6) | 0.081 | 8.4 (1.5) | <0.001 | 3.8 (2.9) | 0.189 | 9.4 (1.5) | <0.001 | 4.8 (2.9) | 0.101 |

**Supplemental Figure. Healthcare Resource Utilization per Person-Year Observeda**



BUP-XR, buprenorphine extended-release monthly injection, for subcutaneous use [CIII]; IDC, individual drug counselling; RR = rate ratio (see note below for calculation)

a Overall, HCRU was low throughout the 6-month study. However, despite this short period, we were able to show a significant decrease in days in hospital with BUP-XR 300/300mg and 300/100mg compared to placebo and a significant decrease in ED visits with BUP-XR 300/300mg compared with placebo. Due to potential differences in follow-up time due to drop-outs, HCRU was analyzed using an incidence-based approach as observed “events” per person-month. In this context, an event may represent hospital bed day, outpatient visit, or other resource utilization. This was calculated as follows:

Incidence (events per 12 person-months) = (Sum of number of events measured between baseline and EOS across all subjects) ÷ (Sum of follow-up days [Baseline date – EOS date +1] across all subjects) \*28\*12

Exact Poisson confidence limits were calculated as follows ([Ulm, 1990](#_ENREF_1)):

       and        

where Y is the observed number of events, YLCL and YUCL are lower and upper confidence limits for Y respectively, and χ2ν,ais the chi-square quantile for upper tail probability on ν degrees of freedom. The point estimate for the incidence was reported in number per person-month; i.e., 28\*Incidence per day; the 95% CI was adjusted similarly.  To compare between placebo and active arms, rate ratios were calculated as the incidence in the active arm divided by the incidence within the placebo arm, with confidence intervals calculated similarly.

**List of Study Investigators**

James L. Andersen, Meridien Research, Lakeland FL; Genie L. Bailey, Stanley Street Treatment and Resources, Inc. (SSTAR), Fall River MA; Scott Robert Bartley, Pillar Clinical Research, LLC, Dallas TX; Michael J. Biunno, Louisiana Research Associates, Inc., New Orleans LA; Care Practice, San Francisco CA; Brent Boyett, Boyett Health Services, Hamilton AL; Jesse M. Carr, Behavioral Research Specialists, LLC, Glendale CA; Eduardo Cifuentes, Carolina Clinical Trials, LLC, Charleston SC; Otto R. Dueno, Midwest Clinical Research Center Dayton OH; Boyde J. Harrison, Haleyville Clinical Research, LLC, Haleyville AL; David R. Hassman, Comprehensive Clinical Research, Berlin NJ; Kent Steven Hoffman, TRY Research, Maitland FL; Valentin Isacesu, North County Clinical Research, Oceanside CA; Saleem Ishaque, SRSD, Inc. DBA Synergy San Diego, National City CA; Rishi Kakar, Innovative Clinical Research, Inc., Lauderhill FL; Kyle Kampman, University of Pennsylvania Treatment Research Center, Philadelphia PA; Richard D. Knapp, IP Shipment and Study Procedures: Aspire Health Partners, Orlando FL; George Konis, Woodland International Research Group, LLC, Little Rock AR; Jelena Kunovac, Altea Research Institute, Las Vegas NV; Joseph A. Kwentus, Precise Research Centers, Flowood MS; Lawrence S. Levinson, Clinical Research Associates of Central PA, Altoona PA; Shishuka Malhotra, Neuro-Behavioral Clinical Research, Inc., Canton OH; Vishaal Mehra, Artemis Institute for Clinical Research, San Diego CA; Ricky Stuart Mofsen and Sandra Daniela Duarte-Sckell, DO St. Louis Clinical Trials, LC, St. Louis MO; Gita Pujari Pahl, Pharmaceutical Professionals, LLC, Oklahoma City OK; Marvin Lane Peyton, Oklahoma Clinical Research Center, Oklahoma City OK; Rakesh Ranjan, Charak Clinical Research Center, Garfield Heights OH; Daniel Rutrick, Adams Clinical Trials LLC, Watertown MA; Gregory Seal, Louisiana Clinical Research, Shreveport LA; Scott Daniel Segal, Scientific Clinical Research, Inc., North Miami FL; Rajinder Shiwach, InSite Clinical Research, DeSoto TX; Haydn Mikel Thomas, Phoenix Medical Research, Inc., Prairie Village KS; Peter Paul Ventre, Research Centers of America, LLC, Oakland Park FL; Amit K. Vijapura, MD, Jacksonville FL; David P. Walling, Collaborative Neuroscience Network, LLC., Garden Grove CA; Katharina L. Wiest, CODA, Inc., Portland OR.

**References Supplemental Text**

Ulm, K. (1990). A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol, 131*(2), 373-375.