**Supplementary Table 1: List of participating Sites**

|  |  |
| --- | --- |
| Innovation Research Institute, Inc. 7171 Coral Way, Suite 307; Miami, FL 33155 | Center for Advanced Medicine & Research 2730 S St. Peters Parkway St. Peters, MO 63303 |
| University Orthopedic Center 101 Regent Court State College, PA 16801 | Western CT Health Network 24 Hospital Avenue Danbury, CT 06810 |
| The OH State University Wexner Medical Center 410 W 10th Avenue N411 Columbus, OH 43210 | Duke University 2301 Erwin Road Durham, NC 27710 |
| Phoenix Clinical Research 7171 North University Drive Tamarac, FL 33321 | Staten Island University Hospital 475 Seaview Ave Staten Island, NY 10305 |
| MS Baptist Medical Center 1225 North State Street Jackson, MS 39202 | Stanford University Dept. of Anesthesia 300 Pasteur Drive Stanford, CA 94305 |
| Harborview Medical Center 325 Ninth Avenue Seattle, WA 98104 | Lotus Clinical Research 100 W CA Boulevard #25 Pasadena, CA 91105 |
| Epic Medical Research 5450 S. Green Street, Suite B Murray, UT 84123 | UVA Health System - Emergency Department 1335 Lee Street, MSB 2266 Charlottesville, VA 22908 |
| Veterans Affairs Medical Center San Francisco- SFVAMC 4150 Clement Street San Francisco, CA 94121 | Albert Einstein Medical Center 5501 Old York Road Korman Bldg. Ground Floor, Suite B-8 Philadelphia, PA 19141 |
| Horizon Research Partners, LLC 3610 Springhill Memorial Drive North Mobile, AL 36608 | Comprehensive Pain Specialists 353 New Shackle Island Road Hendersonville, TN 37075 |
| University of Miami/ Jackson Memorial Hospital 1611 NW 12th Avenue Miami, FL 33136 | Hermann Drive Surgical Hospital 2001 Hermann Drive Houston, TX 77004 |
| Specialist Hospital Shreveport Spine Institute of Louisiana 1500 Line Ave, Suite 206 Shreveport, LA 71101 | Mayo Clinic Hospital 577 East Mayo Boulevard Phoenix, AZ 85054 |
| Samaritan Center for Medical Research 360 Dardanelli Lane, Suite 2G Los Gatos, CA 95032 | Cleveland Clinic Main Campus 9500 Euclid Avenue Cleveland, OH 44195 |
| WA Center for Pain Management 1900 116th Avenue NE Bellevue, WA 98004 | Tampa General Hospital 1 Tampa General Circle, Suite F145 Tampa FL 33606 |
| Christus Santa Rosa Hospital Alamo Heights 1200 Brooklyn Avenue, Suite 150 San Antonio, TX 78209 | University Orthopedic Center 3000 Fairway Drive Altoona, PA 16602 |
| Shoals Medical Trials, Inc. 1300 South Montgomery Avenue Sheffield, AL 35660 | Westside Surgical Hospital 4200 Twelve Oaks Drive Houston, TX 77027 |
| Wake Forest School of Medicine Novant Health Forsyth Med Center 3333 Silas Creek Parkway Winston Salem, NC 27103-3090 | University of South AL Medical Center 2451 Fillingim Street, Suite 101 Mobile, AL 36617 |
| Shoals Clinical Research Associates, LLC 205 Marengo Street Florence, AL 35630 | Pensacola Research Consultants 4700 Bayou Boulevard Pensacola, FL 32503 |
| TX Orthopedic Specialists, PLLC 2425 Highway 121 Bedford, TX 76021 | First Surgical Partners, LLC 4801 Bissonnet Street Bellaire, TX 77401 |
| Health and Life Research Institute, LLC 7801 SW Coral Way, Suite 132 Miami, FL 33155 | Magee-Women's Hospital 300 Halket Street Pittsburgh, PA 15213 |
| Wayne State University - Sinai Grace Hospital 6071 West Outer Drive Detroit, MI 48235  Wayne State University - Detroit Receiving Hospital 4201 St. Antoine Street, UHC 6G Detroit, MI 48201 | Trovare Clinical Research 3838 San Dimas Street, Suite A-280 Bakersfield, CA 93301 |
| Rush University Medical Center 1653 W. Congress Parkway Chicago, IL 60612 |  |

**Supplemental Table 2.** Summary of concomitant medications for nausea, vomiting, and constipation administered after first dose of oliceridine

| Drug Class | No. of Patients (%) | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Cumulative Oliceridine Dose (mg), Group | | | | | |
| ≤4  n=156 | >4 to 8 n=85 | >8 to 16 n=121 | >16 to 36  n=168 | >36  n=238 | All N=768 |
| Peripheral opioid receptor antagonists | 3 (1.9) | 3 (3.5) | 9 (7.4) | 19 (11.3) | 45 (18.9) | 79 (10.3) |
| Propulsives\* | 1 (0.6) | 4 (4.7) | 5 (4.1) | 15 (8.9) | 20 (8.4) | 45 (5.9) |
| Serotonin (5HT3) receptor antagonists | 22 (14.1) | 29 (34.1) | 52 (43.0) | 78 (46.4) | 125 (52.5) | 306 (39.8) |
| Other antiemetics | 16 (10.3) | 15 (17.6) | 26 (21.5) | 30 (17.9) | 49 (20.6) | 136 (17.7) |
| Laxatives | 25 (16.0) | 23 (27.0) | 48 (39.6) | 76 (45.3) | 78 (32.8) | 250 (32.5) |
| Other drugs for constipation | 0 | 0 | 2 (1.7) | 0 | 1 (0.4) | 3 (0.4) |

**\***Metoclopramide and metoclopramide hydrochloride.

**Supplemental Table 3.** Moline Roberts Pharmacologic Sedation Scale (MRPSS) Score 1 “None to Minimal sedation”

| Time point | No. of Patients (%) | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Cumulative Oliceridine Dose (mg), Group | | | | | |
| ≤4  n=156 | >4 to 8  n=85 | >8 to 16  n=121 | >16 to 36  n=168 | >36  n=238 | All N=768 |
| n  Baseline | 148 | 81 | 110 | 160 | 219 | 718 |
| 68  (45.9) | 29  (35.8) | 37  (33.6) | 78  (48.8) | 120 (54.8) | 332 (46.2) |
| n  30 mins after first dose | 84 | 44 | 68 | 94 | 147 | 437 |
| 59  (70.2) | 23  (52.3) | 37  (54.4) | 60  (63.8) | 109 (74.1) | 288 (65.9) |
| n  2.5 hours after first dose | 115 | 60 | 84 | 100 | 124 | 483 |
| 101 (87.8) | 41  (68.3) | 61  (72.6) | 71  (71.0) | 101 (81.5) | 375 (77.6) |
| n  End of treatment | 40 | 23 | 33 | 36 | 39 | 171 |
| 37  (92.5) | 20  (87.0) | 30  (90.9) | 34  (94.4) | 38  (97.4) | 159 (93.0) |

Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.

Percentages are based on the number of patients with a non-missing time point value within each time point and cumulative dose group.

**Supplemental Table 4:** Summary of Subjective opioid withdrawal scale (SOWS) Total Scores

|  | Cumulative Oliceridine Dose (mg), Group | | | | |  | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ≤4   n=156 | >4 to 8  n=85 | >8 to 16  n=121 | >16 to 36  n=168 | >36  n=238 | | All  N=768 |
| SOWS total score, n | 120 | 75 | 109 | 157 | 227 | | 688 |
| Mean (SD) | 3.3 (5.02) | 4.1 (7.76) | 3.9 (4.99) | 4.1 (5.38) | 4.1 (5.77) | | 3.9 (5.69) |
| Total SOWS categories, n (%) | | | | | | | |
| Mild  (total SOWS <17) | 116 (96.7) | 70  (93.3) | 106  (97.2) | 153  (97.5) | 219  (96.5) | | 664  (96.5) |
| Moderate  (total SOWS 17 to 32) | 4  (3.3) | 3  (4.0) | 3  (2.8) | 2  (1.3) | 7  (3.1) | | 19  (2.8) |
| Severe  (total SOWS >32) | 0 | 2  (2.7) | 0 | 2  (1.3) | 1  (0.4) | | 5  (0.7) |

Total SOWS score was derived by summing the individual symptom intensities. If no more than half of the symptoms were missing, imputation with the means score of the nonmissing questions was used to calculate total score. If more than half of the symptoms were missing, the total score was also set to missing.

SD= standard deviation

**Supplemental Figure Legends**

**Supplemental Figure 1.** Overview of design/treatment protocol of the ATHENA study.

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