**Supplementary Figure 1. Consolidated Standards of Reporting Trials Diagram (SPI-611 and SPI-612)**



**Supplementary Figure 2. Consolidated Standards of Reporting Trials Diagram (Pooled Population)**





**SUPPLEMENTAL TABLES**

**Supplemental Table 1. Demographics for Safety Population**

|  | Study SPI-611 |  | Study SPI-612 |  | Pooled Data |
| --- | --- | --- | --- | --- | --- |
| Characteristic/ Category | Apaziquone (n=406) | Placebo (n=396) | Total (n=802) | Apaziquone (n=402) | Placebo (n=410) | Total (n=812) | Apaziquone (n=808) | Placebo (n=806) | Total (n=1614) |
| **Gender, n (%)** |
| Female | 108 (26.6) | 102 (25.8) | 210 (26.2) | 105 (26.1) | 108 (26.3) | 213 (26.2) | 213 (26.4) | 210 (26.1) | 423 (26.2) |
| Male | 298 (73.4) | 294 (74.2) | 592 (73.8) | 297 (73.9) | 302 (73.7) | 599 (73.8) | 595 (73.6) | 596 (73.9) | 1191 (73.8) |
| **Race, n (%)** |
| White | 392 (96.6) | 383 (96.7) | 775 (96.6) | 392 (97.5) | 400 (97.6) | 792 (97.5) | 784 (97.0) | 783 (97.1) | 1567 (97.1) |
| Black or African American | 11 (2.7) | 9 (2.3) | 20 (2.5) | 5 (1.2) | 2 (0.5) | 7 (0.9) | 16 (2.0) | 11 (1.4) | 27 (1.7) |
| Asian | 1 (0.2) | 3 (0.8) | 4 (0.5) | 5 (1.2) | 7 (1.7) | 12 (1.5) | 6 (0.7) | 10 (1.2) | 16 (1.0) |
| Other | 2 (0.5) | 1 (0.3) | 3 (0.4) | 0 | 1 (0.2) | 1 (0.1) | 2 (0.2) | 2 (0.2) | 4 (0.2) |
| **Ethnicity, n (%)** |
| Hispanic/ Latino | 13 (3.2) | 17 (4.3) | 30 (3.7) | 13 (3.2) | 12 (2.9) | 25 (3.1) | 782 (96.8) | 777 (96.4) | 1559 (96.6) |
| Not Hispanic/ Latino | 393 (96.8) | 379 (95.7) | 772 (96.3) | 389 (96.8) | 398 (97.1) | 787 (96.9) | 26 (3.2) | 29 (3.6) | 55 (3.4) |
| **Age, years** |
| Mean (SD) | 67.5 (10.92) | 68.2 (10.72) | 67.8 (10.82) | 66.9 (11.60) | 66.5 (11.83) | 66.7 (11.71) | 67.2 (11.26) | 67.3 (11.32) | 67.2 (11.29) |
| Median (Range) | 68 (29–90) | 68 (32–94) | 68 (29–94) | 68 (24–94) | 68 (22–89) | 68 (22–94) | 68 (24–94) | 68 (22–94) | 68 (22–94) |
| **Age Group, years, n (%)** |
| <65 | 159 (39.2) | 146 (36.9) | 305 (38.0) | 157 (39.1) | 164 (40.0) | 321 (39.5) | 316 (39.1) | 310 (38.5) | 626 (38.8) |
| ≥65 to ≤75 | 140 (34.5) | 139 (35.1) | 279 (34.8) | 144 (35.8) | 146 (35.6) | 290 (35.7) | 284 (35.1) | 285 (35.4) | 569 (35.3) |
| >75 | 107 (26.4) | 111 (28.0) | 218 (27.2) | 101 (25.1) | 100 (24.4) | 201 (24.8) | 208 (25.7) | 211 (26.2) | 419 (26.0) |
| **Smoking Status, n (%)** |
| Current | 95 (23.4) | 80 (20.2) | 175 (21.8) | 116 (28.9) | 97 (23.7) | 213 (26.2) | 211 (26.0) | 177 (22.0) | 388 (24.0) |
| Former | 236 (58.1) | 238 (60.1) | 474 (59.1) | 204 (50.7) | 218 (53.2) | 422 (52.0) | 440 (54.2) | 456 (56.6) | 896 (55.5) |
| Never | 75 (18.5) | 78 (19.7) | 153 (19.1) | 82 (20.4) | 95 (23.2) | 177 (21.8) | 157 (19.3) | 160 (19.9) | 330 (20.5) |
| **Country of Enrollment, n (%)** |
| Canada | 0 | 0 | 0 | 215 (53.5) | 223 (54.4) | 438 (53.9) | 215 (26.6) | 223 (27.7) | 438 (27.1) |
| Poland | 25 (6.2) | 21 (5.3) | 46 (5.7) | 105 (26.1) | 102 (24.9) | 207 (25.5) | 130 (16.1) | 123 (15.3) | 253 (15.7) |
| USA | 381 (93.8) | 375 (94.7) | 756 (94.3) | 82 (20.4) | 85 (20.7) | 167 (20.6) | 463 (57.3) | 460 (57.1) | 923 (57.2) |

SD=standard deviation.

**Supplemental Table 2. Demographics for Target Population**

|  | Study SPI-611 |  | Study SPI-612 |  | Pooled Data |
| --- | --- | --- | --- | --- | --- |
| Characteristic/ Category | Apaziquone (n=295) | Placebo (n=271) | Total (n=566) | Apaziquone (n=282) | Placebo (n=298) | Total (n=580) | Apaziquone (n=577) | Placebo (n=569) | Total (n=1146) |
| **Gender, n (%)** |
| Female | 85 (28.8) | 72 (26.6) | 157 (27.7) | 70 (28.0) | 90 (30.2) | 169 (29.1) |  164 (28.4) |  162 (28.5) |  326 (28.4) |
| Male | 210 (71.2) | 199 (73.4) | 409 (72.3) | 203 (72.0) | 208 (69.8) | 411 (70.9) |  413 (71.6) |  407 (71.5) |  820 (71.6) |
| **Race, n (%)** |
| White | 287 (97.3) | 263 (97.0) | 550 (97.2) | 275 (97.5) | 289 (97.0) | 564 (97.2) | 562 (97.4) | 552 (97.0) | 1114 (97.2) |
| Black or African American | 6 (2.0) | 5 (1.8) | 11 (1.9) | 5 (1.8) | 2 (0.7) | 7 (1.2) | 11 (1.9) | 7 (1.2) | 18 (1.6) |
| Asian | 0 | 2 (0.7) | 2 (0.4) | 2 (0.7) | 6 (2.0) | 8 (4.1) | 2 (0.3) | 8 (1.4) | 10 (0.9) |
| Other | 2 (0.7) | 1 (0.4) | 3 (0.5) | 0 | 1 (0.3) | 1 (0.2) | 2 (0.3) | 2 (0.4) | 4 (0.3) |
| **Ethnicity, n (%)** |
| Hispanic/ Latino | 11 (3.7) | 10 (3.7) | 21 (3.7) | 8 (2.8) | 7 (2.3) | 15 (2.6) | 19 (3.3) | 17 (3.0) | 36 (3.1) |
| Not Hispanic/ Latino | 284 (96.3) | 261 (96.3) | 545 (96.3) | 274 (97.2) | 291 (97.7) | 565 (97.4) | 558 (96.7) | 552 (97.0) | 1110 (96.9) |
| **Age, years** |
| Mean (SD) | 66.9 (11.29) | 67.7 (10.62) | 67.3 (10.97) | 66.6 (11.94) | 65.9 (11.81) | 66.2 (11.87) | 66.8 (11.60) | 66.7 (11.28) | 66.7 (11.44) |
| Median (Range) | 68 (29-90) | 68 (32-94) | 68 (29-94) | 67 (24-94) | 67 (22-89) | 67 (22-94) | 67 (24 - 94) | 68 (22 - 94) | 67 (22 - 94) |
| **Age Group, years, n (%)** |
| <65 | 123 (41.7) | 105 (38.7) | 228 (40.3) | 114 (40.4) | 125 (41.9) | 239 (41.2) | 237 (41.1) | 230 (40.4) | 467 (40.8) |
| ≥65 to ≤75 | 94 (31.9) | 97 (35.8) | 191 (33.7) | 97 (34.4) | 110 (36.9) | 207 (35.7) | 191 (33.1) | 207 (36.4) | 398 (34.7) |
| >75 | 78 (26.4) | 69 (25.5) | 147 (26.0) | 71 (25.2) | 63 (21.1) | 134 (23.1) | 149 (25.8) | 132 (23.2) | 281 (24.5) |
| **Smoking Status, n (%)** |
| Current | 70 (23.7) | 55 (20.3) | 125 (22.1) | 87 (30.9) | 68 (22.8) | 155 (26.7) | 157 (27.2) | 123 (21.6) | 280 (24.4) |
| Former | 173 (58.6) | 152 (56.1) | 325 (57.4) | 138 (48.9) | 155 (52.0) | 293 (50.5) | 311 (53.9) | 307 (54.0) | 618 (53.9) |
| Never | 52 (17.6) | 64 (23.6) | 116 (20.5) | 57 (20.2) | 75 (25.2) | 132 (22.8) | 109 (18.9) | 139 (24.4) | 248 (21.6) |
| **Country of Enrollment, n (%)** |
| Canada | 0 | 0 | 0 | 150 (53.2) | 163 (54.7) | 313 (54.0) | 150 (26.0) | 163 (28.6) | 313 (27.3) |
| Poland | 19 (6.4) | 10 (3.7) | 29 (5.1) | 73 (25.9) | 78 (26.2) | 151 (26.0) | 92 (15.9) | 88 (15.5) | 180 (15.7) |
| USA | 276 (93.6) | 261 (96.3) | 537 (94.9) | 59 (20.9) | 57 (19.1) | 116 (20.0) | 335 (58.1) | 318 (55.9) | 653 (57.0) |

SD=standard deviation.

**Supplemental Table 3. Bladder Cancer History, Tumor Characteristics, and Extent of Exposure for Target Population**

|  | Study SPI-611 |  | Study SPI-612 |  | Pooled Data |
| --- | --- | --- | --- | --- | --- |
| Characteristic/ Category | Apaziquone (n=295) | Placebo (n=271) | Total (n=566) | Apaziquone (n=282) | Placebo (n=298) | Total (n=580) | Apaziquone (n=577) | Placebo (n=569) | Total (n=1146) |
| **Bladder Cancer History, n (%)** |
| Primary | 188 (63.7) | 165 (60.9) | 353 (62.4) | 173 (61.3) | 187 (62.8) | 360 (62.1) | 361 (62.6) | 352 (61.9) | 713 (62.2) |
| Recurrent | 107 (36.3) | 106 (39.1) | 213 (37.6) | 109 (38.7) | 111 (37.2) | 220 (37.9) | 216 (37.4) | 217 (38.1) | 433 (37.8) |
| **Prior Intravesical Therapies, n (%)** |
| Any Prior IVT | 52 (17.6) | 41 (15.1) | 93 (16.4) | 46 (15.6) | 38 (14.0) | 84 (14.5) | 98 (17.0) | 79 (13.9) | 177 (15.4) |
| BCG | 43 (14.6) | 35 (12.9) | 78 (13.8) | 23 (8.2) | 17 (5.7) | 40 (6.9) | 66 (11.4) | 52 (9.1) | 118 (10.3) |
| Mitomycin C | 23 (7.8) | 12 (4.4) | 35 (6.2) | 17 (6.0) | 20 (6.7) | 37 (6.4) | 40 (6.9) | 32 (5.6) | 72 (6.3) |
| Other IVT | 2 (0.7) | 7 (2.6) | 9 (1.6) | 14 (5.0) | 12 (4.0) | 26 (4.5) | 16 (2.8) | 19 (3.3) | 35 (3.1) |
| **Tumor Lesion Number at Baseline, n (%)** |
| 1 lesion | 191 (64.7) | 181 (66.8) | 372 (65.7) | 167 (59.2) | 181 (60.7) | 348 (60.0) | 358 (62.0) | 362 (63.6) | 720 (62.8) |
| 2 lesions | 51 (17.3) | 54 (19.9) | 105 (18.6) | 65 (23.0) | 53 (17.8) | 118 (20.3) | 116 (20.1) | 107 (18.8) | 223 (19.5) |
| 3 lesions | 42 (14.2) | 26 (9.6) | 68 (12.0) | 31 (11.0) | 49 (16.4) | 80 (13.8) | 73 (12.7) | 75 (13.2) | 148 (12.9) |
| 4 lesions | 11 (3.7) | 10 (3.7) | 21 (3.7) | 19 (6.7) | 15 (5.0) | 34 (5.9) | 30 (5.2) | 25 (4.4) | 55 (4.8) |
| **Tumor Grade at Baseline, n (%)** |
| G1 | 218 (73.9) | 190 (70.1) | 408 (72.1) | 207 (73.4) | 234 (78.5) | 441 (76.0) | 425 (73.7) | 424 (74.5) | 849 (74.1) |
| G2 | 77 (26.1) | 81 (29.9) | 158 (27.9) | 75 (26.6) | 54 (21.5) | 139 (24.0) | 152 (26.3) | 145 (25.5) | 297 (25.9) |
| **Largest Tumor Lesion Size at Baseline** |
| Mean (SD) | 1.7 (0.93) | 1.7 (0.95) | 1.7 (0.94) | 1.6 (0.86) | 1.6 (0.85) | 1.6 (0.85) | 1.7 (0.90) | 1.6 (0.90) | 1.6 (0.90) |
| Median (Range) | 1.5 (0.2-3.5) | 1.5 (0.2-3.5) | 1.5 (0.2-3.5) | 1.5 (0.3-3.5) | 1.5 (0.2-3.5) | 1.5 (0.2-3.5) | 1.5 (0.2-3.5) | 1.5 (0.2-3.5) | 1.5 (0.2-3.5) |
| **Time from End of TURBT to Start of Treatment Instillation, n (%)** |
| ≤30 minutes | 134 (45.4) | 145 (53.5) | 279 (49.3) | 99 (35.1) | 78 (26.2) | 177 (30.5) | 233 (40.4) | 223 (39.2) | 456 (39.8) |
| 31-90 minutes | 60 (20.3) | 39 (14.4) | 99 (17.5) | 57 (20.2) | 61 (20.5) | 118 (20.3) | 117 (20.3) | 100 (17.6) | 217 (18.9) |
| >90 minutes | 101 (34.2) | 87 (32.1) | 188 (33.2) | 126 (44.7) | 159 (53.4) | 285 (49.1) | 227 (39.3) | 246 (43.2) | 473 (41.3) |
| **Volume of Instillate, n (%)** |
| <40 mL | 0 | 2 (0.7) | 2 (0.4) | 0 | 1 (0.3) | 1 (0.2) | 0 | 3 (0.5) | 3 (0.3) |
| =40 mL | 295 (100.0) | 269 (99.3) | 564 (99.6) | 282 (100.0) | 295 (99.0) | 577 (99.5) | 577 (100.0) | 564 (99.1) | 1141 (99.6) |
| >40 mL | 0 | 0 | 0 | 0 | 2 (0.7) | (0.3) | 0 | 2 (0.4) | 2 (0.2) |
| **Duration of Retention, n (%)** |
| <60 minutes | 8 (2.7) | 5 (1.8) | 13 (2.3) | 5 (1.8) | 4 (1.3) | 9 (1.6) | 13 (2.3) | 9 (1.6) | 22 (1.9) |
| =60 minutes | 252 (85.4) | 246 (90.8) | 498 (88.0) | 240 (85.1) | 253 (84.9) | 493 (85.0) | 492 (85.3) | 499 (87.7) | 991 (86.5) |
| >60 minutes | 35 (11.9) | 20 (7.4) | 55 (9.7) | 37 (13.1) | 41 (13.8) | 78 (13.4) | 72 (12.5) | 61 (10.7) | 133 (11.6) |

IVT=Intravesical Therapy; BCG=Bacillus Calmette–Guérin; SD=standard deviation.

**Supplemental Table 4. Summary of Adverse Events – Safety Population**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Characteristic/Category | SPI‑611 |  | SPI‑612 |  | Overall |
| Apaziquone (n=406) | Placebo(n=396) |  | Apaziquone(n=402) | Placebo(n=410) |  | Apaziquone(n=808) | Placebo(n=806) |
| Any Treatment-Related TEAE | 51 (12.6) | 50 (12.6) |  | 42 (10.4) | 40 (9.8) |  | 93 (11.5) | 90 (11.2) |
| **Dysuria** | 20 (4.9) | 19 (4.8) |  | 17 (4.2) | 14 (3.4) |  | 37 (4.6) | 33 (4.1) |
| **Bladder Spasm** | 8 (2.0) | 5 (1.3) |  | 3 (0.7) | 4 (1.0) |  | 11 (1.4) | 9 (1.1) |
| **Micturition Urgency** | 5 (1.2) | 13 (13.3) |  | 6 (1.5) | 3 (0.7) |  | 11 (1.4) | 16 (2.0) |
| **Bladder Pain** | 5 (1.2) | 3 (0.8) |  | 5 (1.2) | 1 (0.2) |  | 10 (1.2) | 4 (0.5) |
| **Hematuria** | 1 (0.2) | 12 (3.0) |  | 7 (1.7) | 2 (0.5) |  | 8 (1.0) | 14 (1.7) |
| **Urinary Tract Infection** | 4 (1.0) | 1 (0.3) |  | 4 (1.0) | 0 |  | 8 (1.0) | 1 (0.1) |
| **Pollakiuria** | 4 (1.0) | 10 (2.5) |  | 2 (0.5) | 5 (1.2) |  | 6 (0.7) | 15 (1.9) |