Sufentanil Sublingual Tablet System 15mcg vs IV PCA Morphine: A Comparative Analysis of Patient Satisfaction and Drug Utilization by Surgery Type

2016 European Society of Regional Anesthesia Congress
Maastricht, Netherlands

Karen P. DiDonato, MSN, RN
Sufentanil Sublingual Tablet System Phase 3 Program (SSTS 15mcg; Zalviso®)

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Phase #</th>
<th>Clintrials.gov NCT #</th>
<th>Patient Population</th>
<th>Current Study Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAP310</td>
<td>Phase 3 pivotal</td>
<td>NCT0153962</td>
<td>Post-operative, major abdominal</td>
<td>Published 2014¹</td>
</tr>
<tr>
<td>IAP311</td>
<td>Phase 3 pivotal</td>
<td>NCT01660763</td>
<td>Post-operative, major joint replacement</td>
<td>Published 2015²</td>
</tr>
<tr>
<td>IAP309</td>
<td>Phase 3 head-to-head</td>
<td>NCT01539538</td>
<td>Post-operative, major abdominal or joint replacement</td>
<td>Published 2014³</td>
</tr>
<tr>
<td>IAP312</td>
<td>Phase 3 open label</td>
<td>NCT02662764</td>
<td>Post-operative, all</td>
<td>Ramp-up</td>
</tr>
</tbody>
</table>

- Received MAA approval in late 2015; currently available in Germany, France, UK, Belgium, Netherlands and Italy

¹Ringold et al., Regional Anesthesia and Pain Medicine, 2014
²Jove et al., Anesthesiology, 2015
³Melson et al., Pain Practice, 2014
SSTS Controlled Studies
Design

- Two randomized, double-blind, placebo-controlled trials to evaluate efficacy and safety of SSTS for treatment of post-operative pain
  - IAP310 - Major open abdominal surgery
  - IAP311 - Unilateral knee or hip replacement

- One randomized, open-label, active comparator trial to evaluate efficacy and safety of SSTS compared to Intravenous Patient Controlled Analgesia with morphine (IV PVA MS) for treatment of post-operative pain
  - IAP309 - Open abdominal or major joint replacement surgery (randomized 1:1 SSTS:IV PCA MS, 177:180)
IAP309 Objective

Study Objective

- Demonstrate non-inferiority of SSTS compared to IV PCA MS
  - Patients randomized to receive either SSTS (15mcg with a 20-minute lockout) or IV PCA MS (1mg with a 6-minute lockout) for management of post-operative pain, through 48 hours
    - Patients could remain in the trial through 72 hours if needed
  - If the lower boundary of the 95% CI around differences in “success” was not less than -15%, SSTS treatment was considered non-inferior to the IV PCA MS treatment
IAP309 Study Design

**Outcome Measures**

### Primary Efficacy Endpoint
- Patient global assessment (PGA) of method of pain control measured on 4-pt categorical scale (1 = poor; 4 = excellent)
- “Success” was defined as the proportion of patients who responded “good” or “excellent”

### Key Secondary Efficacy Endpoints
- Percent of patients dropping out due to inadequate analgesia
- Healthcare professional Global Assessment (HPGA)
- Use of rescue medication

### Safety Endpoints
- Adverse events
- Vital signs
- Sedation level
- Concomitant medication use
- Blood samples for PK were collected at 24 and 48-hours
### IAP309 Inclusion/Exclusion

#### Inclusion
- Male and female patients 18 years and older
- ASA class I-III
- General or spinal anesthesia that did not include intrathecal opioids
- Moderate to severe pain in the immediate post-operative period
  - score of > 4 on 0-10 NRS

#### Key Exclusion
- Opioid tolerant (>15mg oral MSO₄ equivalent daily)
- Positive urine drug screen
- Documented sleep apnea or requiring supplemental oxygen
- Use of perioperative regional anesthetic techniques
- Premedication with long-acting opioids
- Patients who presented with respiratory difficulties or intractable vomiting in the PACU
Results: Disposition & Baseline Characteristics

Demographics

- 359 randomized; 357 dosed (ITT)
- Baseline characteristics equally distributed
- Mean age: SSTS 63.8 years vs IV PCA MS 64.0 years
- Surgery Type n(%)
  - 161 (45.2%) hip replacement [83 SSTS; 78 IV PCA MS]
  - 116 (32.6%) knee replacement [56 SSTS; 60 IV PCA MS]
  - 79 (22.2%) major abdominal [37 SSTS; 42 IV PCA MS]

Reasons for early termination:

<table>
<thead>
<tr>
<th>Reason</th>
<th>SSTS (%)</th>
<th>IV PCA MS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>7.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>7.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Other</td>
<td>2.8</td>
<td>5.6</td>
</tr>
</tbody>
</table>
Results: Primary Efficacy (PGA-48)

- A higher proportion of SSTS patients (78.5%) responded “good” or “excellent” on the PGA48 compared to IV PCA MS patients (65.6%).
- This difference was statistically significant for both non-inferiority ($p < 0.001$) and superiority ($p = 0.007$).
# Results: Safety

<table>
<thead>
<tr>
<th>Related Adverse Events*</th>
<th>SSTS (n=177)</th>
<th>IV PCA MS (n=180)</th>
<th>Total (n=357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>76 (42.9%)</td>
<td>72 (40.0%)</td>
<td>148 (41.5%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (13.0%)</td>
<td>20 (11.1%)</td>
<td>43 (12.0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (11.3%)</td>
<td>15 ( 8.3%)</td>
<td>35 ( 9.8%)</td>
</tr>
<tr>
<td>O2 saturation decreased</td>
<td>17 ( 9.6%)</td>
<td>17 ( 9.4%)</td>
<td>34 ( 9.5%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>11 ( 6.2%)</td>
<td>20 (11.1%)</td>
<td>31 ( 8.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 ( 7.9%)</td>
<td>12 ( 6.7%)</td>
<td>26 ( 7.3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 ( 5.6%)</td>
<td>6 ( 3.3%)</td>
<td>16 ( 4.5%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 ( 4.0%)</td>
<td>14 ( 7.8%)</td>
<td>21 ( 5.9%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6 (3.4%)</td>
<td>2 (1.1%)</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (1.1%)</td>
<td>5 (2.8%)</td>
<td>7 (2.0%)</td>
</tr>
</tbody>
</table>

*Adverse events ≥ 2.5% in either cohort and considered by the Investigator to be “possibly” or “probably” related to study drug (CSR Table 33)
IAP309: PGA “Success” over 48-hours by Surgery Type

* p≤0.01 (non-inferiority and superiority based on z-test)
** p<0.01 (non-inferiority)
IAP309: Drug Utilization 0-24hrs Post-op by Surgery Type

All SSTS Patients - 24hrs

* p=0.004 for the overall comparison among treatment groups
IAP309: Drug Utilization Over 48-hours by Surgery Type

All SSTS Patients

Sufentanil Sublingual Tablet System

*1 Zalviso Drug Cartridge contains 40 sufentanil sublingual 15mcg tablets

N=84
N=56
N=37

1 cartridge*
IAP309: Summary of Number of Sufentanil Doses Used by Surgery Type

All Patients – 48hrs

<table>
<thead>
<tr>
<th>Total Number of Tablets Used</th>
<th>Hip</th>
<th>Knee</th>
<th>Abdominal</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>27.4</td>
<td>17.9</td>
<td>10.7</td>
</tr>
<tr>
<td>24-47</td>
<td>32.4</td>
<td>38.1</td>
<td>28.6</td>
</tr>
<tr>
<td>48-71</td>
<td>27</td>
<td>35.7</td>
<td>23.8</td>
</tr>
<tr>
<td>72-120</td>
<td>27</td>
<td>28.6</td>
<td>16.1</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>1.8</td>
<td>10.8</td>
<td>10.8</td>
</tr>
</tbody>
</table>
IAP309: Drug Utilization
48-hour Completers

Patients completing 48-hrs

Sufentanil Sublingual Tablet System

*1 Zalviso Drug Cartridge contains 40 sufentanil sublingual 15mcg tablets
IAP309: Equianalgesia SSTS vs. IV PCA MS

Mean # Doses and Opioid Equivalent

* Assumes standard morphine PCA syringe of 30ml
Conclusion

- In this study of post-operative patients, SSTS demonstrated both non-inferiority and statistical superiority compared to IV PCA MS for Patient Global Assessment.
- PGA-48 subgroup analysis by surgery type also indicated that SSTS provided “good” or “excellent” pain relief for most patients following joint replacement or major abdominal surgery.
- SSTS AE reports were similar to IV PCA MS.
- Drug utilization data suggests that, on average, knee replacement patients will require more doses of sublingual sufentanil (15mcg) to manage their pain post-operatively compared with abdominal or hip replacement patients.
  - These differences may be clinically significant in the first 24 hours.
Thank you

Karen DiDonato
kdidonato@acelrx.com