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

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Sufentanil Sublingual Tablet System Phase 3 Program (SSTS 15mcg; Zalviso®)

Study Number	Phase #	Clintrials.gov NCT #	Patient Population	Current Study Status
IAP310	Phase 3 pivotal	NCT0153962	Post-operative, major abdominal	Published 2014[1]
IAP311	Phase 3 pivotal	NCT01660763	Post-operative, major joint replacement	Published 2015[2]
IAP309	Phase 3 head-to-head	NCT01539538	Post-operative, major abdominal or joint replacement	Published 2014[3]
IAP312	Phase 3 open label	NCT02662764	Post-operative, all	Ramp-up

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

[1]Ringold et al., *Regional Anesthesia and Pain Medicine*, 2014
[2]Jove et al., *Anesthesiology*, 2015
[3]Melson et al., *Pain Practice*, 2014

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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 MSO_4 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]

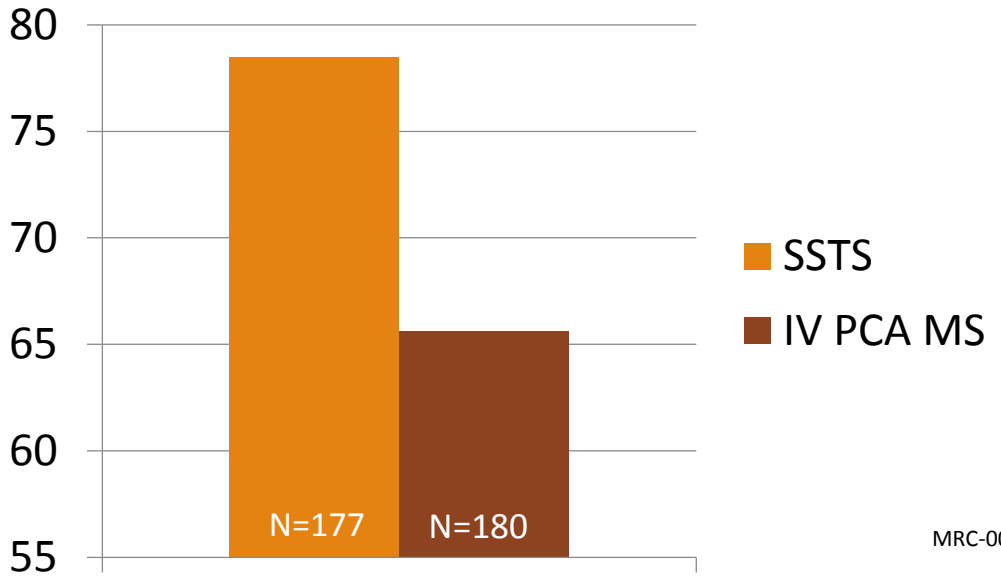
Reasons for early termination:

	SSTS (%) n=177	IV PCA MS (%) n=180
Adverse event	**7.3**	**10.0**
Lack of efficacy	**7.3**	**8.9**
Other	**2.8**	**5.6**

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 ($p = 0.007$).

Percent “Success” on Patient Global Assessment (PGA)



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Results: Safety

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

*Adverse events ≥ 2.5% in either cohort and considered by the Investigator to be "possibly" or "probably" related to study drug (CSR Table 33)

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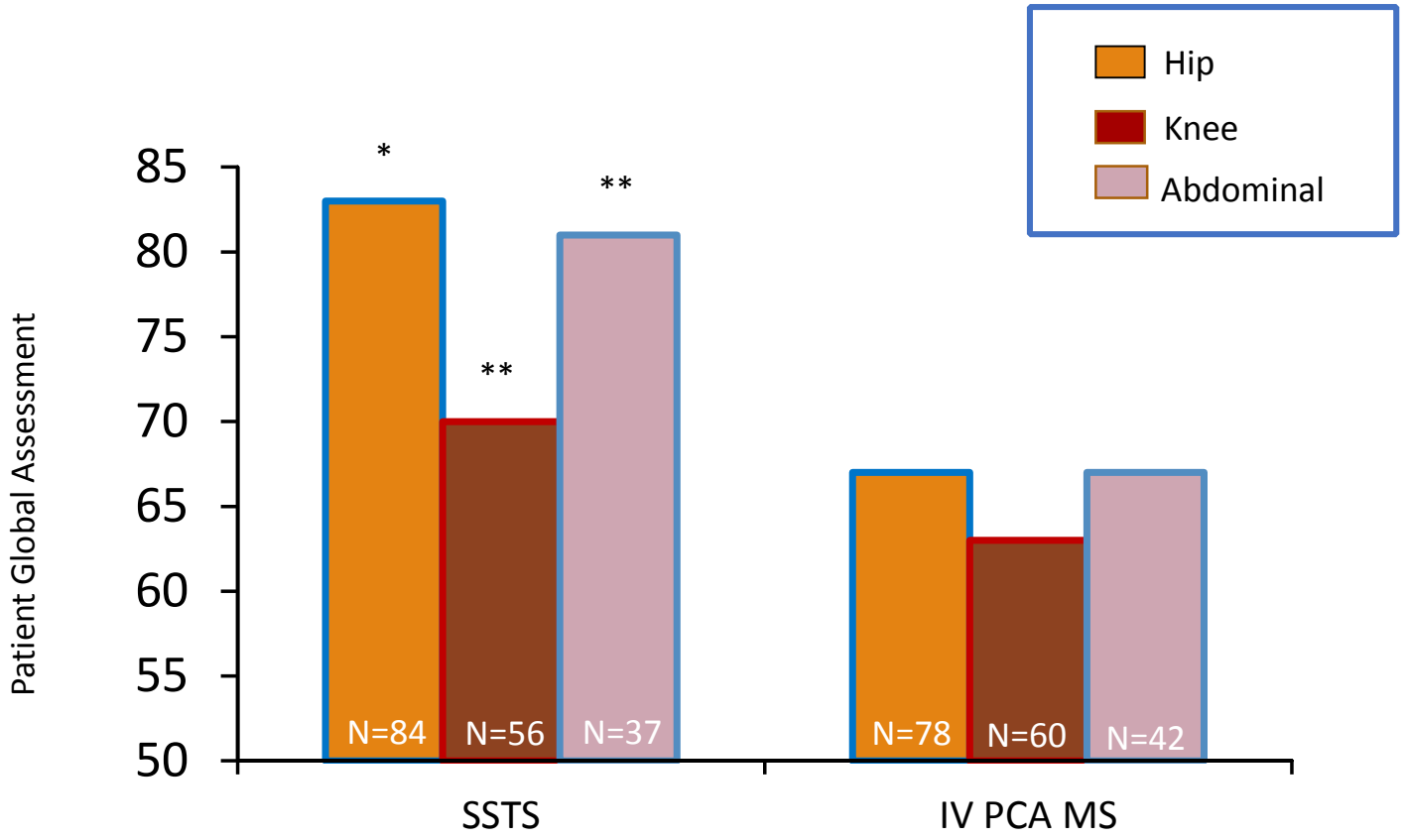
IAP309: PGA "Success" over 48-hours by Surgery Type



* p≤0.01 (non-inferiority and superiority based on z-test)
** p<0.01 (non-inferiority)

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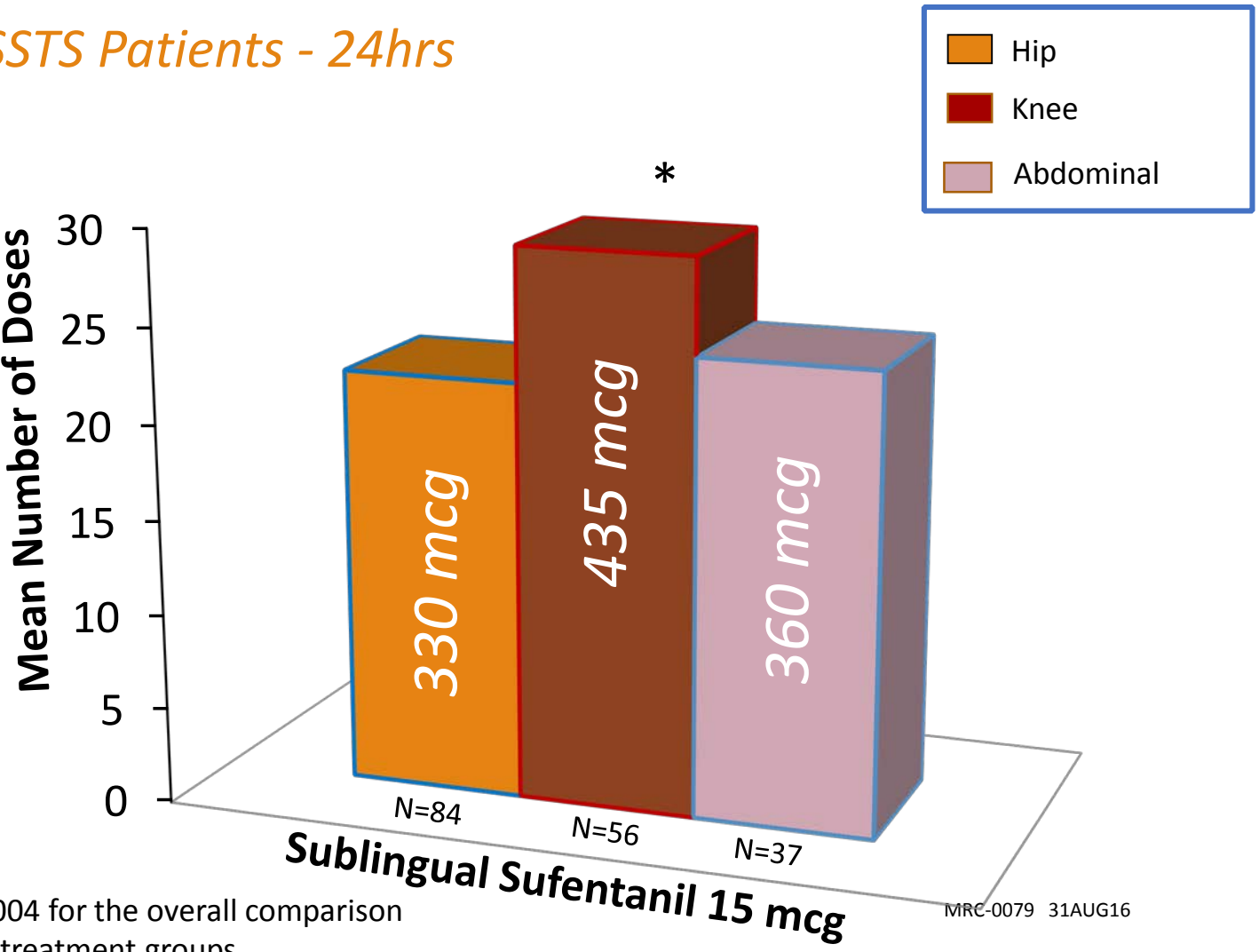
IAP309: Drug Utilization 0-24hrs Post-op by Surgery Type

All SSTS Patients - 24hrs



* p=0.004 for the overall comparison among treatment groups

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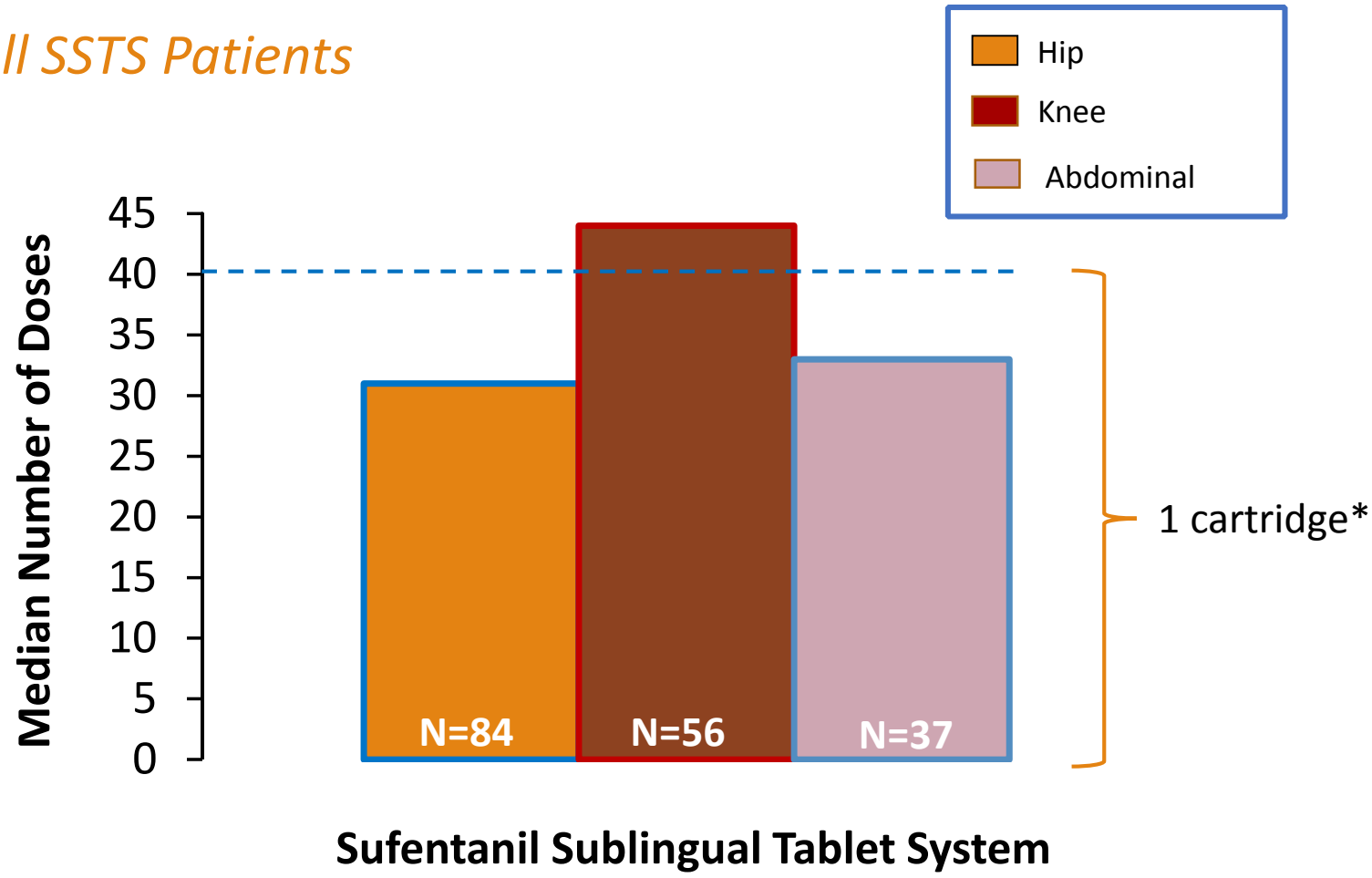
IAP309: Drug Utilization Over 48-hours by Surgery Type

All SSTS Patients



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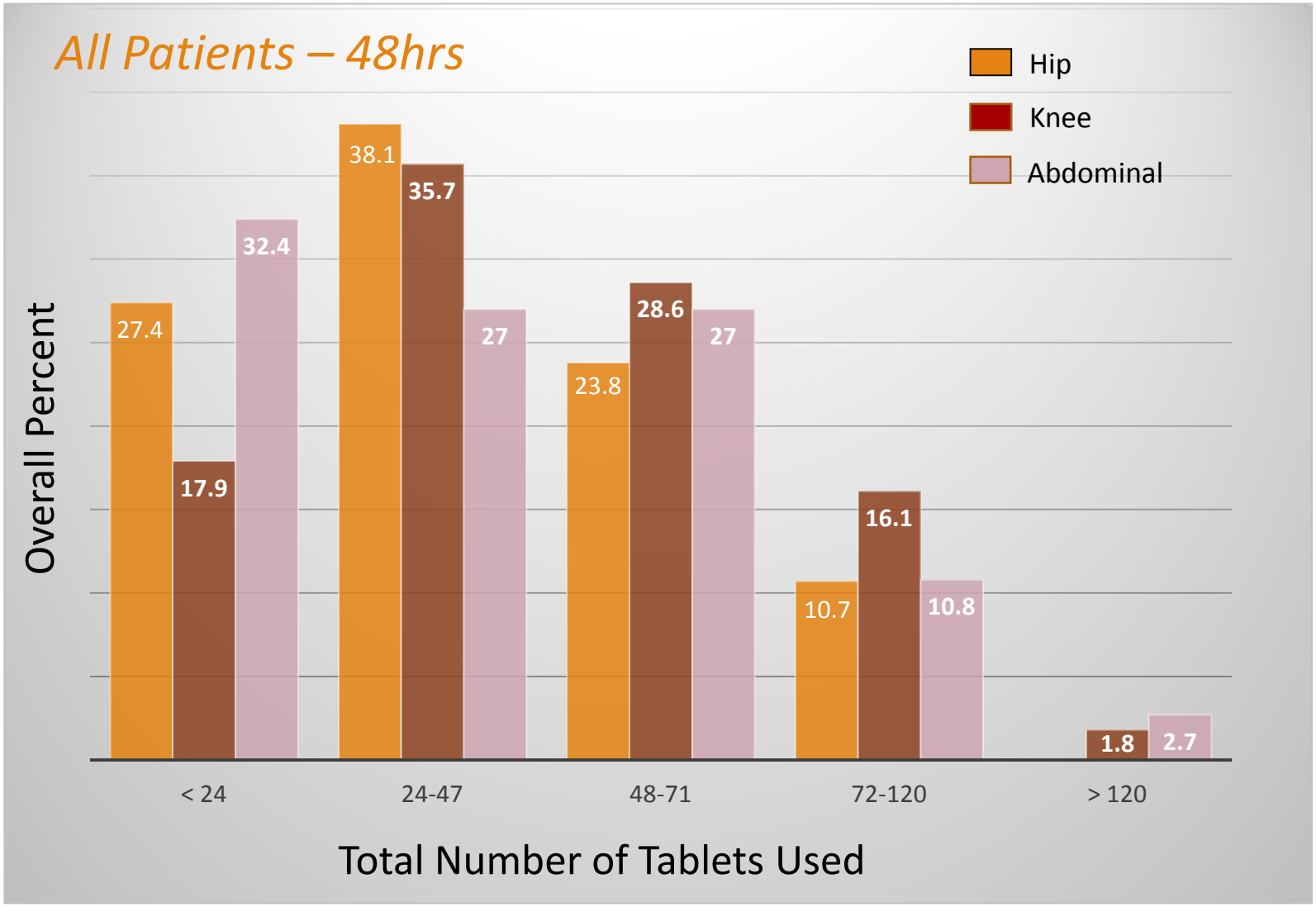
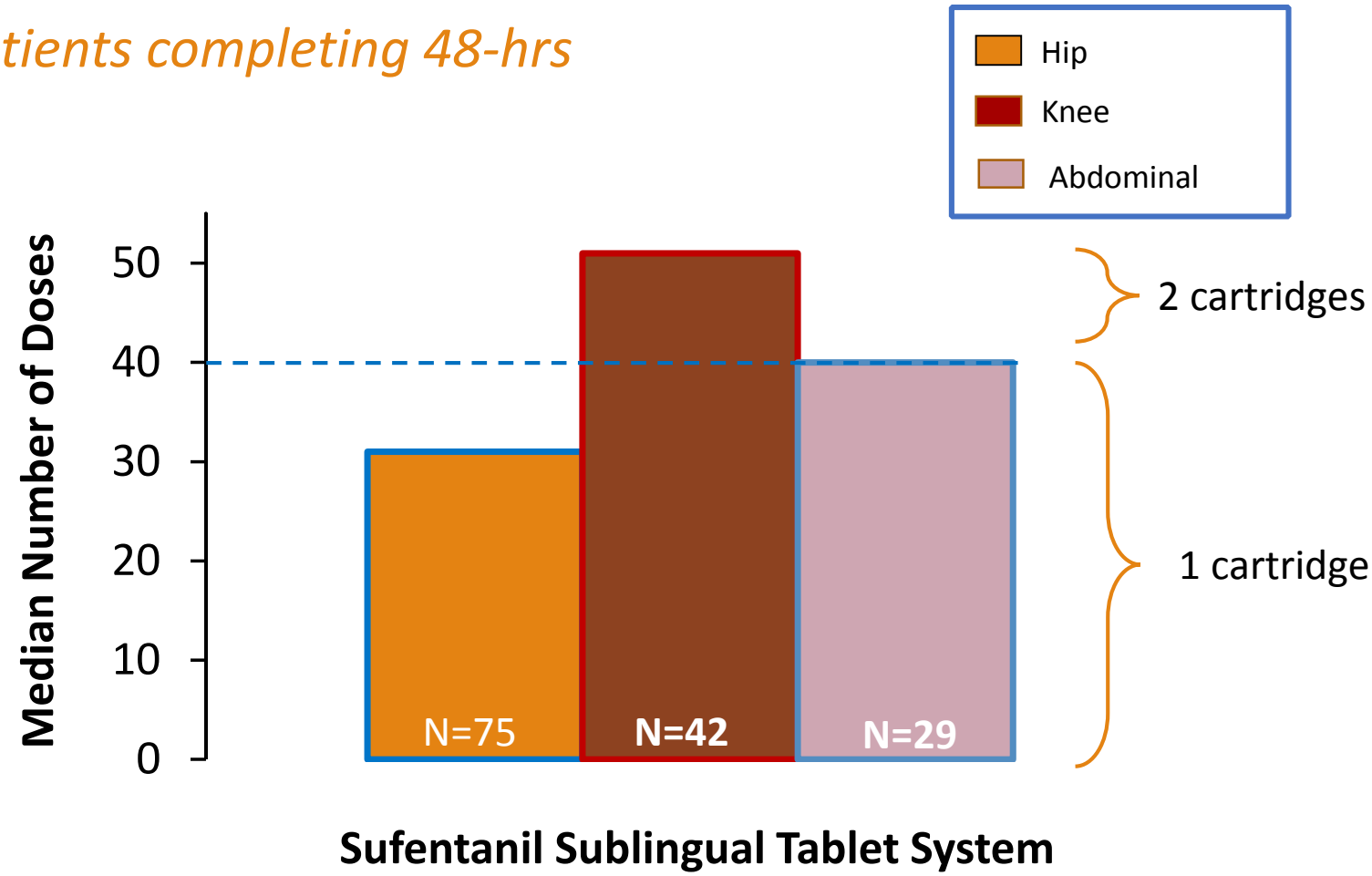
*1 Zalviso Drug Cartridge contains 40 sufentanil sublingual 15mcg tablets

IAP309: Summary of Number of Sufentanil Doses Used by Surgery Type



IAP309: Drug Utilization 48-hour Completers

Patients completing 48-hrs



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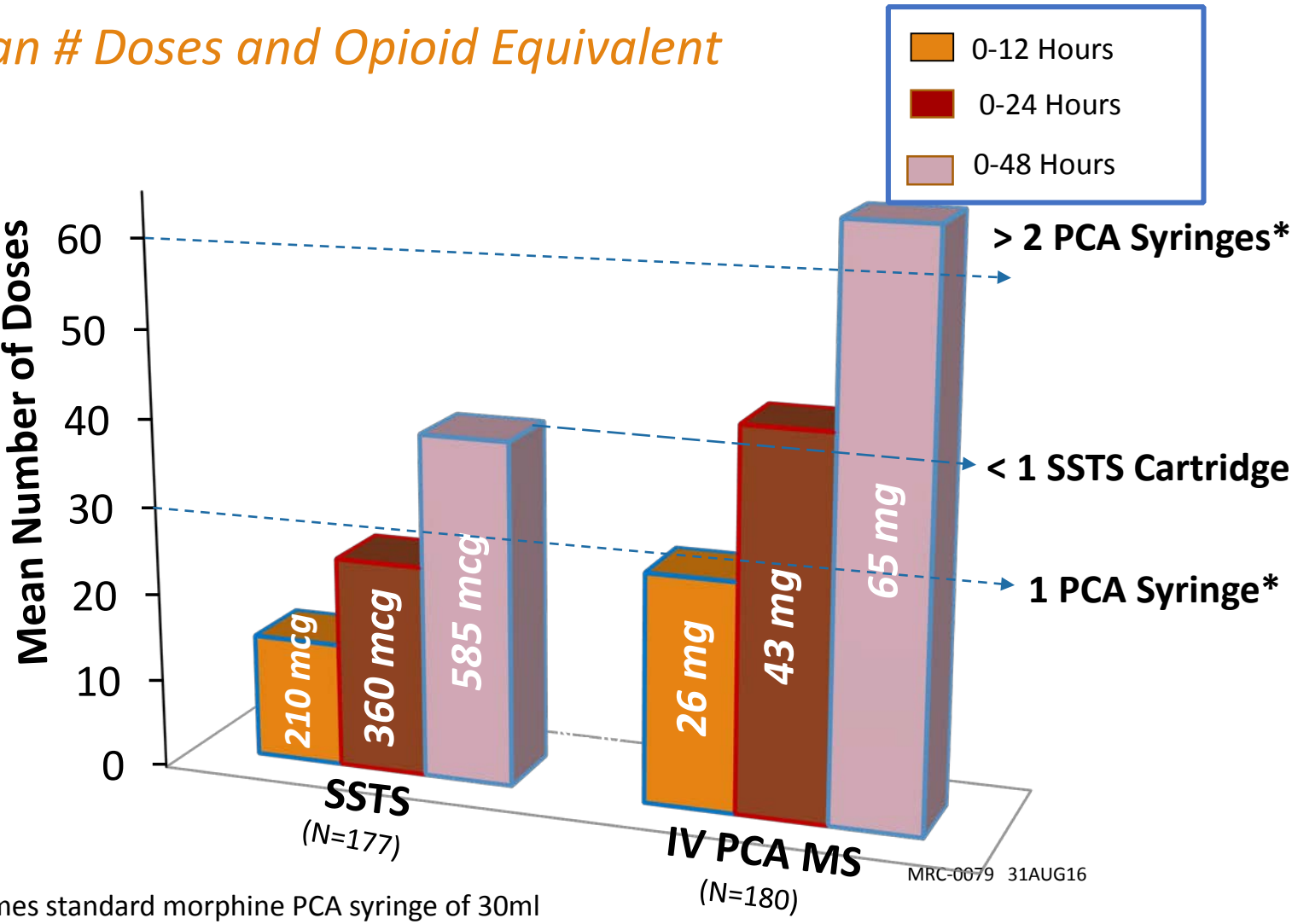
IAP309: Equianalgesia SSTS vs. IV PCA MS

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

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