Full Proposal

Study Title: Use of Dsuvia in Patients Undergoing Spine Surgery

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Background:

Dsuvia is a novel drug recently approved by the FDA (2018) for moderate to severe acute pain. It has a unique mode of delivery as a small sublingual tablet (Figure 1), and there is evidence to suggest it may provide significant benefit to surgical patients with moderate to severe pain. Based on published data as well as recently completed studies, there is strong evidence to suggest that DSUVIA can decrease other opioid consumption including long-acting opioids in major surgery, provide better pain control, and decrease PACU length of stay and earlier discharges.

Sufentanil, unlike morphine and hydromorphone, avoids the issue of active metabolites that can lead to prolonged, untoward effects, which can complicate postoperative care and affect patient discharge. A study by Minkowitz et al[1] found that sufentanil sublingual tablet (SST, Disuvia) 30 mcg was well tolerated, with no unexpected adverse events, no clinically meaningful vital sign changes, and a safety profile that was as expected for this postoperative patient population. In addition, Miner et al[2] studied the use of SST in the emergency department and found that SST was a potentially feasible option for managing moderate-to-severe acute pain in that setting. A study by Meijir et al[3] studied adult patients undergoing major surgery in five hospitals in the Netherlands who received the SSTS for postoperative pain relief as part of multimodal pain management. The authors showed that the SSTS effectively managed postoperative pain in abdominal and orthopedic surgeries. A study by Melson et al[4], a randomized, open-label

noninferiority study that enrolled patients scheduled for elective major open abdominal or orthopedic surgery assessed the proportion of patients who responded “good” or “excellent” at the 48-hour timepoint on the Patient Global Assessment (PGA48) of method of pain control. The results showed that 78.5% vs. 65.6% of patients achieved PGA48 "success" for SSTS vs. IV PCA morphine, respectively, demonstrating non-inferiority as well as statistical superiority for treatment effect. Patients using SSTS reported more rapid onset of analgesia and patient and nurse ease of care and satisfaction scores were higher than IV PCA morphine. Adverse events were similar between the 2 groups, and SSTS had fewer patients experiencing oxygen desaturations below 95% compared to IV PCA morphine Future studies are needed to determine patient populations that benefit most from the SSTS, assess the added values versus intravenous patient-controlled analgesia, and determine the pharmacoeconomics of the system[3].

More recently, a study by Cassavaugh K et al.[5] analyzed data from a hospital comparing 140 DSUVIA-treated patients with 157 matched historical controls. DSUVIA was dosed either 30 minutes before the end of surgery for longer surgeries or just prior to induction for shorter surgeries. Patients were a combination of inpatient and outpatients (same-day surgery). The data shows an overall 56% decrease in PACU IV morphine milligram equivalents (mean MME ± SE) opioid requirements compared to control group receiving typical IV opioids (8.1 ± 0.5 to 3.6 ± 0.4; $p<0.001$). The PACU Phase 1 discharge time also was significantly decreased compared to the control group (80 ± 2 min vs 66 ± 2 min; $p<0.001$). From a safety perspective, 3 patients out of 157 required naloxone in the PACU to reverse respiratory depression in the control group and no naloxone was required in the DSUVIA group. PACU time is estimated to cost between $6-$8 per minute, therefore the time saved more than pays for the drug and can increase efficiency and possibly caseload. The investigator’s conclusion is that DSUVIA is a high therapeutic index opioid that has an extended duration of action into the PACU period thereby either

avoiding opioids completely in the PACU in many patients (48.5% of patients in the DSUVIA group vs 16.6% of patients in the control group), or significantly decreasing the amount of IV opioids required in the PACU and therefore decreasing PACU discharge time.

Another recent study, by Tvetenstrand CD et al.[6] was conducted in a hospital with ambulatory abdominal surgery patients with DSUVIA dosed 30 minutes prior to induction. A total of 47 patients were in the DSUVIA arm and 81 matched historical controls were compared. This study showed a decrease in overall IV opioid requirements and a decreased Phase 1 PACU time. No patients required naloxone for respiratory depression in either group.

Sufentanil is a drug with a rapid onset (15 min) and high potency (30 mg= morphine 5mg) (pka = 8.0 and solubility coefficient greater than 2000). It is highly bioavailable and highly lipophilic with a high therapeutic opioid index (LD50/ED50). It has a much lower Cmax compared with IV sufentanil. It reaches 70 % Cmax in 30 minutes, lasting as long as 3 hours. Based on existing outcomes data, we hypothesize that there will be a clinically significant difference in spine surgery patients as compared to the historical controls.

Purpose:

In this study we plan to examine the perioperative use of Dsuvia (sufentanil SL; FDA approval 2018) in the analgesic regimen for spine surgery, one of the most common surgeries performed in the US. Patients undergoing spinal fusion surgery often experience significant pain during the first three postoperative days[7]. Currently, no data are available for this patient population which routinely experiences moderate to severe acute pain requiring significant opioid use. We will analyze whether Dsuvia (sufentanil SL) is associated with lower pain scores, frequency of rescue

opioids, lower overall opioid consumption, PACU and hospital length of stay, and side effects of opioid use (i.e., nausea, vomiting, constipation, respiratory effects).

Hypotheses:

1. The perioperative use of Dsuvia 30 mcg SL in a prospectively recruited cohort of patients undergoing spine surgery will be associated with lower postoperative numeric rating scale pain scores (NRS; primary outcome) than observed in two historical control groups that did not receive Dsuvia: one group that received intraoperative remifentanil infusion and one that received intraoperative sufentanil infusion.

2. The perioperative use of Dsuvia (sufentanil SL) will be associated with lower overall opioid consumption, lower frequency of rescue opioids, lower PACU and hospital length of stay, and fewer side effects of opioid use (i.e., nausea, vomiting, constipation, respiratory complications) than observed in two historical control groups of patients receiving remifentanil or sufentanil infusions without perioperative Dsuvia.

Methods:

The study design is an Observational Longitudinal (OL) study with historical controls. There will be 1 prospectively recruited study arm (patients receiving the study drug Dsuvia) and 2 historical control arms (one that received an intraoperative remifentanil infusion and the other that received an intraoperative sufentanil infusion, both without Dsuvia).

Inclusion criteria:

Patients undergoing spine surgery (1-3 levels) who are opioid-naïve (no opioid use 30 days prior to surgery), 18-75 years old, ASA physical status 1-3.

Exclusion criteria:

Microdiscectomy, chronic opioid users, significant respiratory depression, acute or severe bronchial asthma, chronic lung disease, known or suspected gastrointestinal obstruction including paralytic ileus, liver disease (defined as alkaline phosphatase (ALP) > 56, aspartate aminotransferase (AST)> 100), known allergy or hypersensitivity to sufentanil or its components, baseline dementia, serotonin syndrome, adrenal insufficiency, severe hypotension, increased intracranial pressure, brain tumors, head injury, impaired consciousness, malignant hyperthermia, ASA physical status >3, age >75, pregnant patients.

IV. STUDY SCHEMA:

Patients undergoing spine surgery (1 or more levels)

Observational Longitudinal (Study) ARM	RETROSPECTIVE (Control) ARM
↓	↓
Preoperative Phase	intraoperative sufentanil infusion (80 pts) **and** intraoperative remifentanil infusion (80 pts)
<u>Screening for Eligibility Criteria</u>: informed consent demographics history and physical concomitant medications	
↓	
Patient Recruitment (ie. Study Arm, target: 25pts)	
↓	

Dsuvia 30mcg SL

↓

Intraoperative Phase
General endotracheal anesthesia (TIVA with propofol/sufentanil)
Standardized anesthetic technique (see protocol below)
Dsuvia x1 prior to emergence from anesthesia

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Postoperative Phase
Pain scores (NRS) q15 min up to 2 hrs
Concomitant Medication use/opioid consumption
Dsuvia prn q1hr as 1st line (NRS >3); Fentanyl prn as 2nd line, or 1st line if repeat Dsuvia cannot yet be given and NRS is >3 (see PACU schema below)
Up to 3 doses of Dsuvia may be administered in the PACU (each at least 1 hr apart)

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Hospitalization Phase
Follow up during inpatient hospital stay
Concomitant Medication use/pain scores
Both arms: standard of care analgesia (PO and IV prn)
Quality of Recovery (QoR); patient satisfaction (study arm only)

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Post-discharge Phase
Follow up following discharge
Prescription opioid use

Outcomes:

Primary:
Mean postoperative pain scores (PACU)

Secondary:
Mean postoperative pain scores (inpatient)
opioid consumption (MMEs, PACU and inpatient)
Frequency of opioid rescue medications given
PACU LOS (min)
hospital LOS (days)
nausea, vomiting, constipation, respiratory events
sedation level (PACU)
quality of recovery (QoR 15)
utilization of prescription opioids following discharge

As shown above, the following secondary outcomes will also be collected in the Study cohort to obtain estimates that can be used to power future randomized controlled trials: sedation level, quality of recovery (QoR-15)[8], patient satisfaction score (satisfaction with the level of pain control, 6-point scale[4]), and utilization of prescription opioids following discharge.

Safety assessments will include adverse events (AEs) and use of concomitant medications, periodic monitoring of vital signs (blood pressure, heart rate, and respiratory rate), and continuous monitoring of oxygen saturation in the PACU.

Detailed Clinical Protocol

Preoperative:

The surgeon will approach the patient and introduce the study and one of the investigators will explain the study to the patient. The surgeon will assess subject at their visit. At this visit, the surgeons will identify any patients that may benefit from Dsuvia. The information will be provided to one of the investigators. The investigator will subsequently review their eligibility and inclusion criteria. If the subject continues to meet all the criteria, the investigator will explain the study with the patient. Thereafter the patients will be provided the consent forms for their review and a 24/7 contact number for any questions regarding this study. All patient questions will be answered and informed consent will be obtained by one of the investigators who is a licensed physician listed on the protocol. The patient will be provided contact information. A co-investigator will be available to answer

questions on a 24 hour basis. It will be explained to the patient that they will be permitted to withdraw from the study at any time for any reason until their day of surgery. On arrival at the preoperative area, the patient will be assigned a code by one of the investigators. Prior to premedication, all patients will be made familiar with the use of numeric rating scale (NRS): 0-10 (no pain to the worst pain imaginable). The baseline NRS score will be recorded. All routine standard practices for surgery, anesthesia, and perioperative care will be followed with the exception of the study intervention. All patients will be premedicated with midazolam (0.025-0.05 mg/kg)

Intraoperative Management:

The Study arm will receive general endotracheal anesthesia (GETA). Anesthesia induction will be achieved with propofol (1.5-2.5mg/kg), succinylcholine (1mg/kg), and Fentanyl (50-100 mcg) bolus. Anesthesia maintenance will consist of TIVA (total intravenous anesthesia) with continued infusions of propofol (80-200 mcg/kg/min) and sufentanil (0.2-0.3mcg/kg/hr). The study group will receive Dsuvia 30 mcg at surgery end, administered by the anesthesiologist, timed to occur prior to emergence from anesthesia, and after the patient is turned supine. Antiemetic prophylaxis will be administered (ondansetron) per standard practice. The patient will then be transferred to the PACU.

Postoperative Management:

Note that Dsuvia will be ordered as q1hr prn, meaning that repeat doses must be administered at least 1 hr apart (up to 3 doses can be administered in the PACU).

Postoperative pain scores will be recorded by the PACU nurse and the research assistant. This will be obtained by using NRS scale every 15 mins up to 2 hours.

In the PACU, patients will be ordered to receive Dsuvia 30 mcg q1 hr prn for breakthrough pain (for NRS > 3) as the 1st line analgesic, with fentanyl as the rescue analgesic if the patient is still experiencing pain (NRS >3). The following opioid administration schema will be used for pain management in the PACU:

- 1st line: Dsuvia SL 30mcg (NRS >3). 2nd line: Fentanyl 25-50mcg (NRS >3)
- If upon arrival to the PACU the patient is still experiencing pain with NRS >3 but cannot yet receive a repeat dose of Dsuvia (because of having received 1st dose in the OR less than 1 hour ago), then the patient can receive fentanyl 25-50mcg prn until eligible to receive Dsuvia.
- If at any time the patient's NRS >3 after 20 min following an administration of either Dsuvia or fentanyl, the patient can receive a repeat dose of fentanyl until again eligible to receive Dsuvia.

Once the patient is transferred to the floor, both groups will receive the standard of care postoperative pain management orders (ie PO and IV prn analgesia for NRS > 3).

Patients who require additional doses of Dsuvia will be monitored for respiratory depression for at least one hour after the last administration of the drug dose.

Sample Size/Statistical analysis:

The primary outcome is nurse-collected mean pain scores. Assuming a within-group standard deviation in PACU NRS pain score of 2.5 points[7], enrollment of 30 patients in the study group and inclusion of at least 80 patients in each retrospective control group will provide at least 80% power at a two sided alpha level of 0.025 (0.05/2 pair-wise comparisons) to detect a minimal clinically important difference of 2 points[9] between the Study group and each of the retrospective groups using linear regression.

To account for any potential lack of comparability in baseline characteristics between patients in the Study and retrospective groups, all outcomes will be compared between the prospective group and each of the retrospective groups using doubly robust estimation incorporating both multivariable linear regression adjustment and inverse probability of treatment weights based on the propensity score[10]. Doubly robust estimation will allow for unbiased treatment effect estimates even if one of the two models (i.e., propensity score model or outcome model) is miss-specified. The multivariable linear regression models for the outcomes will adjust for the following covariates: age, sex, BMI, ASA class, surgical invasiveness tier, reoperation, history of anxiety, anxiolytic use, history of depression, and antidepressant use. Analytic weights will be based on the inverse of the propensity score, calculated via logistic regression as the probability of being in the Dsuvia group conditional upon the aforementioned covariates included in the multivariable outcome model.

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References

1. Minkowitz HS, Leiman D, Melson T, Singla N, DiDonato KP, Palmer PP. Sufentanil Sublingual Tablet 30 mcg for the Management of Pain Following Abdominal Surgery: A Randomized, Placebo-Controlled, Phase-3 Study. *Pain Pract.* 2017;17:848-858.

2. Miner JR, Rafique Z, Minkowitz HS, DiDonato KP, Palmer PP. Sufentanil sublingual tablet 30mcg for moderate-to-severe acute pain in the ED. *Am J Emerg Med.* 2018;36:954-961.

3. Meijer F, Cornelissen P, Sie C, et al. Sublingual sufentanil for postoperative pain relief: first clinical experiences. *J Pain Res.* 2018;11:987-992.

4. Melson TI, Boyer DL, Minkowitz HS, et al. Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, active-comparator trial. *Pain Pract.* 2014;14:679-688.

5. Cassavaugh K et al. Outcomes of Disuvia in patients undergoing major surgery. Manuscript in Preparation, 2020. Source: AcelRx Pharmaceuticals.

6. Tvetenstrand CD et al. Prospective study of preoperative DSUVIA for ambulatory surgery. Manuscript in preparation 2020. Source: AcelRx Pharmaceuticals.

7. Murphy GS, Szokol JW, Avram MJ, et al. Clinical Effectiveness and Safety of Intraoperative Methadone in Patients Undergoing Posterior Spinal Fusion Surgery: A Randomized, Double-blinded, Controlled Trial. *Anesthesiology.* 2017;126:822-833.
8. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology.* 2013;118:1332-1340.
9. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 2001;94:149-158.
10. Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *Am J Epidemiol.* 2011;173:761-767.

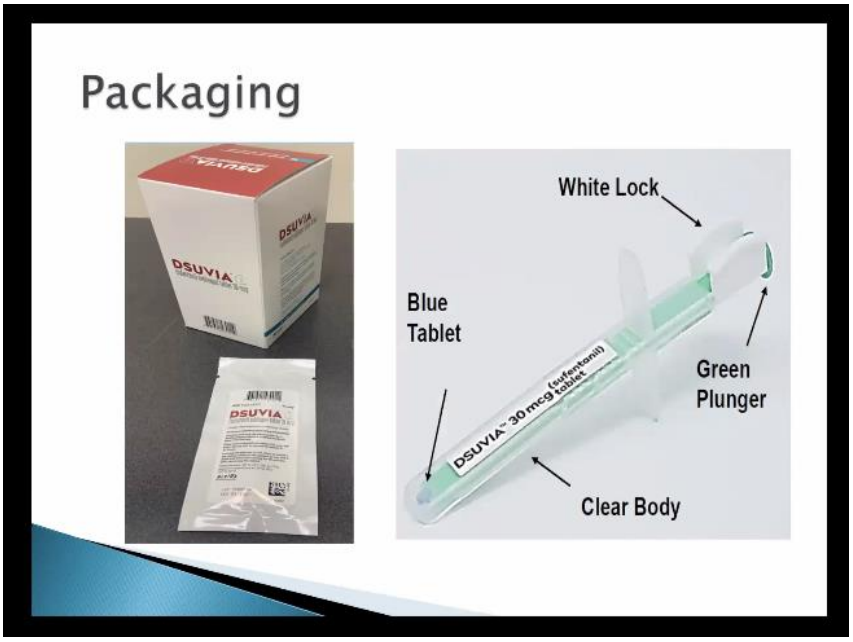

Figure 1: Packing and components of Dsuvia (Sufentanil SL)