Intravenous Oliceridine and Opioid-related Complications:

The VOLITION Multicenter Pilot Cohort Study

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Background

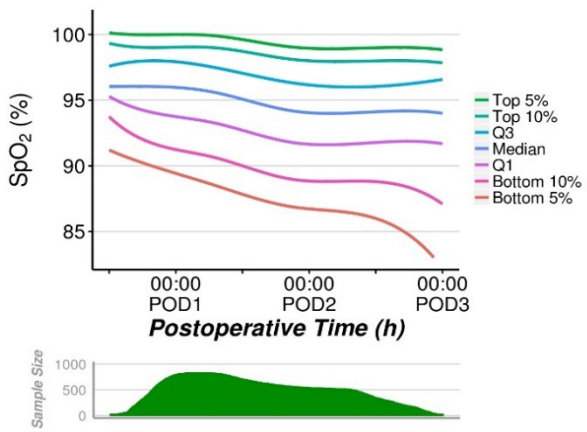
When patients having major surgery reach the post-anaesthesia care unit, families naturally assume that they have survived the most dangerous part of the perioperative experience. Their assumption is wrong. Mortality in the 30 days after surgery is more than 100 times higher than intraoperative mortality.[1,2] In fact, if the month after surgery were considered a disease, it would be the third leading cause of death in the United States.[3]

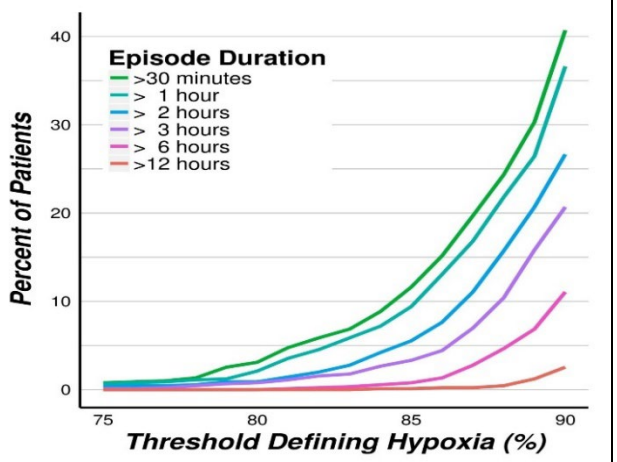
Most 30-day postoperative mortality occurs during the initial hospitalization, that is, under direct medical care in our highest-level facilities. The most common causes of 30-day postoperative mortality are major bleeding which cannot easily be prevented, and cardiopulmonary complications which possibly can be.[4] Respiratory complications are also common — and are of special interest because nearly all are preventable.[5]

Ward respiratory compromise

The reported incidence of ward respiratory compromise is 0.3% to 3.4% when defined by interventions such as naloxone administration,[6] but is 21% when defined by prolonged oxygen desaturation[7] and 41% when defined by bradypnea episodes.[8] Frighteningly, nearly all these events are missed by routine 4-hour nursing checks.[7]

We quantified hypoxemia on the surgical wards using blinded continuous saturation monitoring (n=833). Postoperative hypoxemia was common, serious, and prolonged (**Fig. 1**). For example, 20% of patients demonstrated an average of 10 minutes of saturation <90% *per hour over their entire hospitalization* (**Fig. 2**). And soberingly, 90% of serious hypoxemic episodes (saturation <90% for ≥1 full hour) were completely missed by nurses conducting routine vital sign monitoring at four-hour intervals.[7]





Figures. 1 and 2. Continuous *blinded* saturation monitoring in 850 patients recovering from non-cardiac surgery. The figure on the left shows that by the second postoperative day, more than 10% of all saturation measurements were <90%. The figure on the right shows that desaturation was common, profound, and prolonged. For example, 10% of patients had a continuous hour of saturation ≤85%. Nursing vital sign monitoring at 4-hour intervals missed more than 90% of these episodes.[7]

We recently finished PRediction of Opioid-induced respiratory depression In patients monitored by capnoGraphY (PRODIGY), a prospective, observational study of continuous capnography and oximetry conducted in the United States, Europe, and Asia.[8] The cohort included patients who were given parenteral opioids and continuously monitored with oximetry and capnography in surgical wards. Monitor alarms and data were blinded. Respiratory compromise episodes were defined by respiratory rate ≤5 bpm for ≥3 minutes; oxygen saturation ≤85% for ≥3 minutes; end-tidal carbon dioxide ≤15 or ≥60 mmHg for ≥3 minutes; apnea episode lasting >30 seconds; or any respiratory Opioid-Related Adverse Events (rORADE). One or more respiratory compromise episodes were detected in 614 (46%) of 1,335 patients continuously monitored for a median of 24 hours. Compared to patients without respiratory depression episodes, mean hospital length of stay was 3 days longer in patients with ≥1 respiratory depression episode using continuous oximetry and capnography monitoring. Opioid-Related Adverse Events were observed in only 22 patients, and more than half were hypoxemic.

Various risk factors for developing respiratory depression have been reported for post-surgical patients including sleep apnea, obesity, snoring, old age, post-surgery, increased opioid dose requirement, concomitant use of other sedating medications, comorbidities like preexisting pulmonary or cardiac disease, PCA use and smoking.[1,4,7,16,17] Nonetheless, postoperative respiratory events remain difficult to predict. For example, we have shown that STOP-BANG scores (a measure of obstructive sleep apnea risk) are not associated with the amount of postoperative oxygen desaturation (**Fig. 3**).[9] Similarly, risk was not reduced by using short-acting opioids in patient controlled analgesia systems (**Fig. 4**).[10]

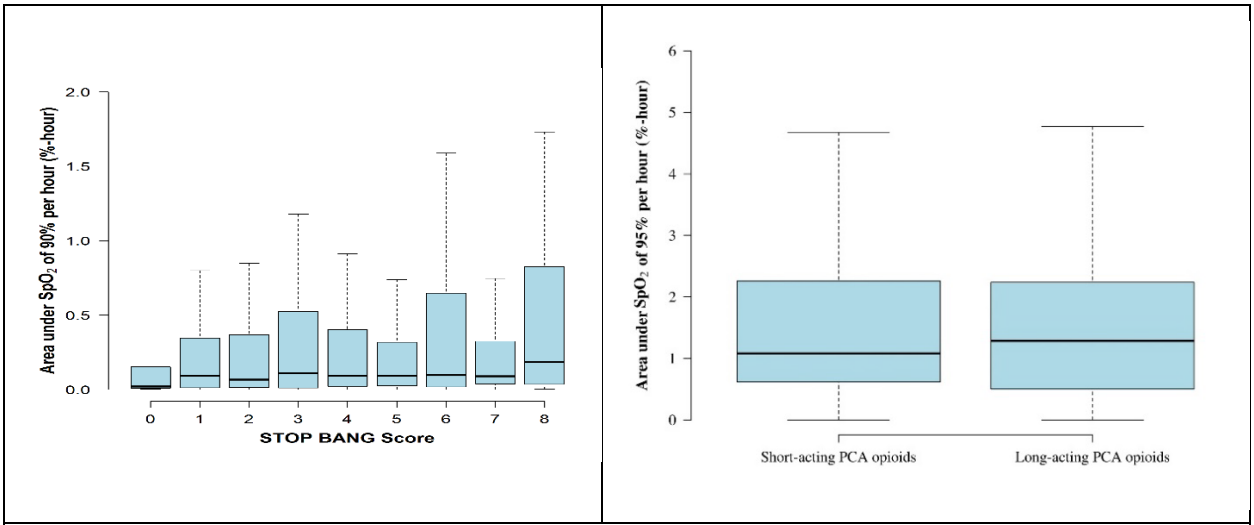


Figure. 3 (left). STOP-BANG scores (a measure of obstructive sleep apnea risk) are not associated with the amount of postoperative oxygen desaturation.[9] **Fig. 4 (right)**. Hypoxemia risk was not reduced by using short-acting opioids in patient-controlled analgesia systems.[10]

In PRODIGY, age, male sex, opioid naivety, sleep disorder breathing, and chronic heart failure were the biggest drivers of opioid induced respiratory depression episodes

detected by continuous monitoring. However, the adjusted area under the receiver-operating characteristics curve was only 0.74. Available information thus indicates that it is difficult to reliably predict which postoperative inpatients will exhibit respiratory compromise or the severity of these episodes. A corollary is that all patients need to be continuously monitored to reliably detect respiratory compromise early enough to intervene effectively and presumably prevent serious complications.

The role of opioids

Opioid analgesia remains the primary pharmacologic intervention for managing pain in hospitalized patients.[11] However, up to 80% of patients who received opioid analgesics experience Opioid-Related Adverse Drug Events (ORADEs).[4] The Joint Commission on Hospital Accreditation identifies improper patient monitoring as one of the main causes of ORADEs.[1,5]

Opioid-induced respiratory depression is traditionally defined using surrogate measures, such as hypoventilation with or without oxygen desaturation, and is often a diagnosis of exclusion[12] and is probably much under-estimated.[13,14] Opioid-related adverse events, including respiratory depression, are associated with increased length of stay (mean five additional days), readmission (15.8% vs 9.4% in patients without events), and cost (mean increase $10,000).[15,16]

Oliceridine: A novel biased G-protein-coupled opioid

Conventional opioids signal through the μ-receptor, a G-protein-coupled receptor found in both the CNS as well as the gastrointestinal tract. This signaling produces the familiar beneficial analgesic effects of opioids, as well as a number of adverse effects, including respiratory depression, euphoria, nausea, vomiting, and constipation. Many studies have shown that opioids exhibit multiple signaling pathways. In particular, in addition to signaling through the GPCR pathway, opioids also signal through the β-arrestin pathway, which not only attenuates the GPCR response, but also elicits distinct responses in its own right, many of which are considered to be complications (**Fig. 5**).

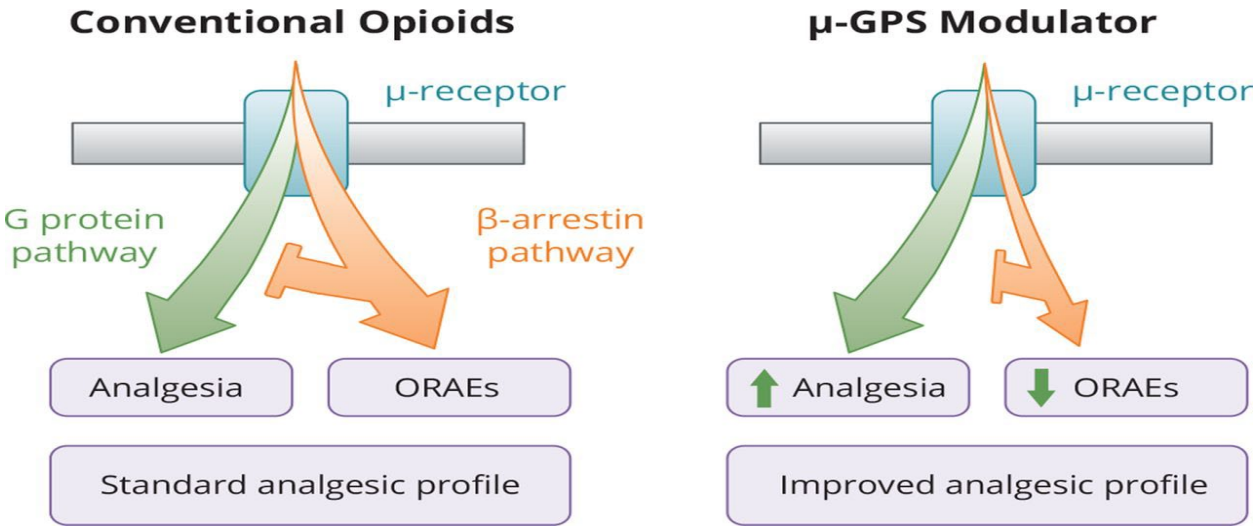


Figure. 5. G-coupled mechanism (right) provides analgesia, potentially with fewer side effects.

Bohn and colleagues showed that in β-arrestin 2 knockout mice, the analgesic response to morphine was greatly enhanced, and showed little attenuation as compared to wild-type mice.[17] Rahael and colleagues showed that the respiratory depression and constipation effects typically observed with morphine were greatly reduced in β-arrestin knockout mice as compared to wild-type mice.[18] These data suggest that a μ-receptor agonist which preferentially signals through the GPCR pathway might exhibit fewer adverse effects than an agonist which signals through both pathways. A "biased" opioid could have great potential in reducing the adverse event profile typically observed with this class of drugs.

Oliceridine is a biased μ-receptor agonist designed to preferentially signal through the GPCR pathway, and exhibits much less β-arrestin signaling than morphine in cultured HEK cells (**Fig. 6**). Oliceridine showed potent analgesic activity (similar to morphine) in both mice and rat models of analgesia, while also exhibiting less respiratory depression and constipation than morphine.[19]

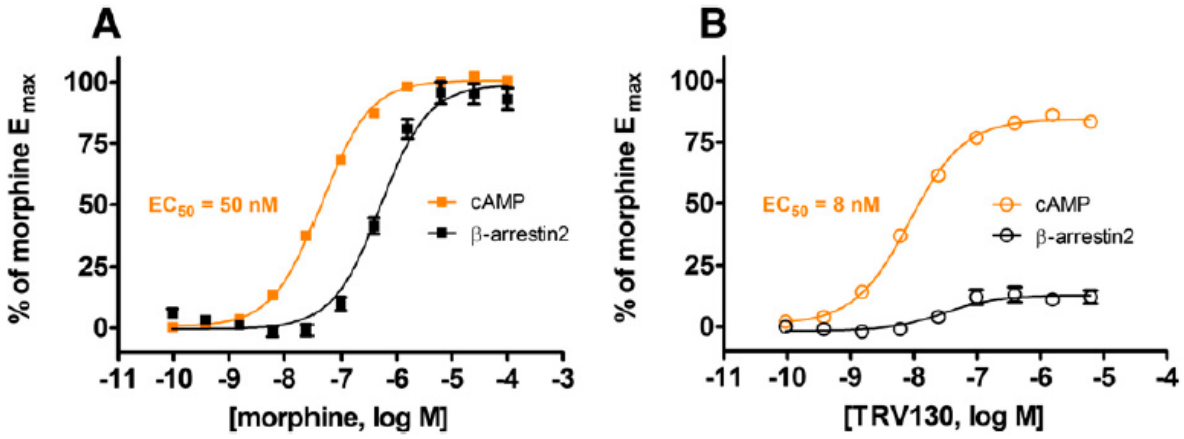


Figure 6. Oliceridine (TRV130) shows greatly reduced β-arrestin signaling as compared with morphine in HEK cells.[19]

In a Phase 1 study examining the pharmacokinetics and pharmacodynamics of oliceridine in healthy volunteers, the analgesic response (as measured by the cold pain test) showed a clear dose response and a faster onset of effect than morphine (**Fig. 7**), while exhibiting a similar nadir of respiratory depression (measured by the ventilatory response to hypercapnia) at equipotent doses. Importantly, the respiratory effects of oliceridine at all doses quickly returned to baseline levels, while morphine exhibited a depressed respiratory response for the duration of the study (**Fig. 8**).

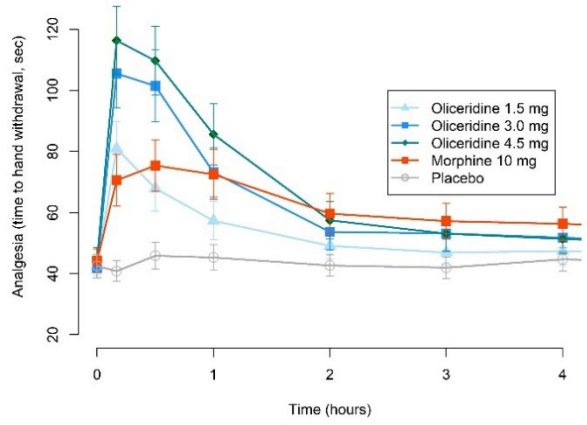


Figure. 7. Oliceridine 1.5 mg exhibits similar levels of analgesia as compared to morphine 10 mg, but with a shorter onset of action.

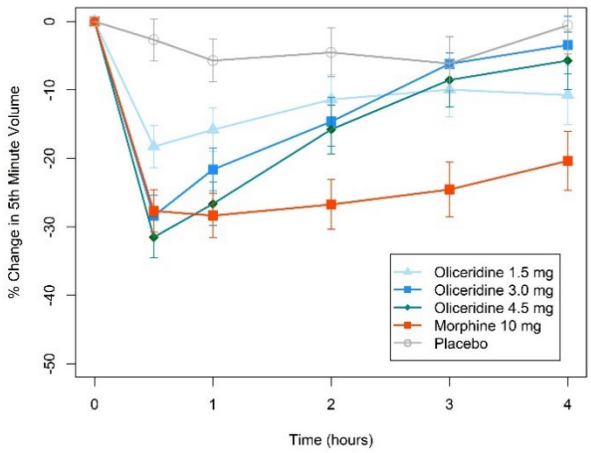


Figure. 8. Oliceridine 3 mg shows comparable nadir effects on respiratory depression to morphine 10 mg, but quickly returns to baseline levels. In contrast, the depressant effects of morphine last for the duration of the experiment.

In the Phase 3 program, oliceridine at all doses produced significantly more analgesia than placebo and was comparable to morphine (**Fig. 9**), while producing less respiratory depression as measured by oxygen desaturation (**Table 1**) and less nausea and vomiting (**Fig. 10**).

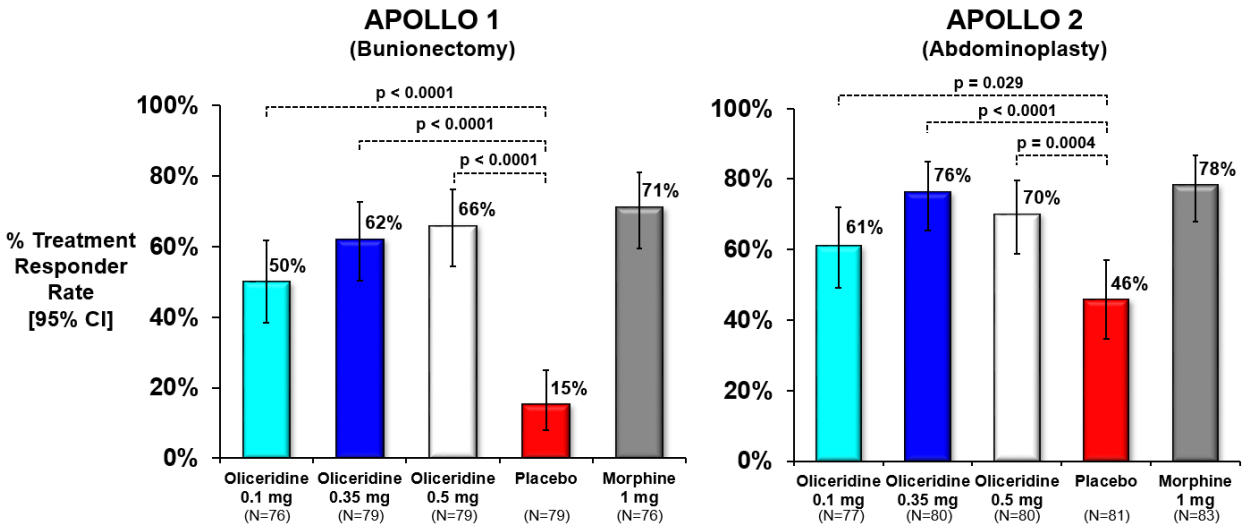


Figure. 9. Primary Endpoint Results in APOLLO 1 and APOLLO 2.

Safety Parameter	Incidence (%)				Relative Reduction (p-value)	
	Oliceridine			Morphine 1 mg N=158		
	0.1 mg N=153	0.35 mg N=158	0.5 mg N=159		0.1 mg vs Morphine	0.35 mg vs Morphine
O_2 saturation < 90%	5.9	14.6	17.0	22.2	73% (< 0.001)	34% (0.11)
Dosing interruption	3.9	14.6	17.6	24.7	83% (< 0.001)	41% (0.033)
Supplemental O_2	4.6	14.6	17.6	22.8	80% (< 0.001)	36% (0.083)

Table 1. Oxygen Desaturations and Clinician Interventions in Controlled Phase 3 Studies.

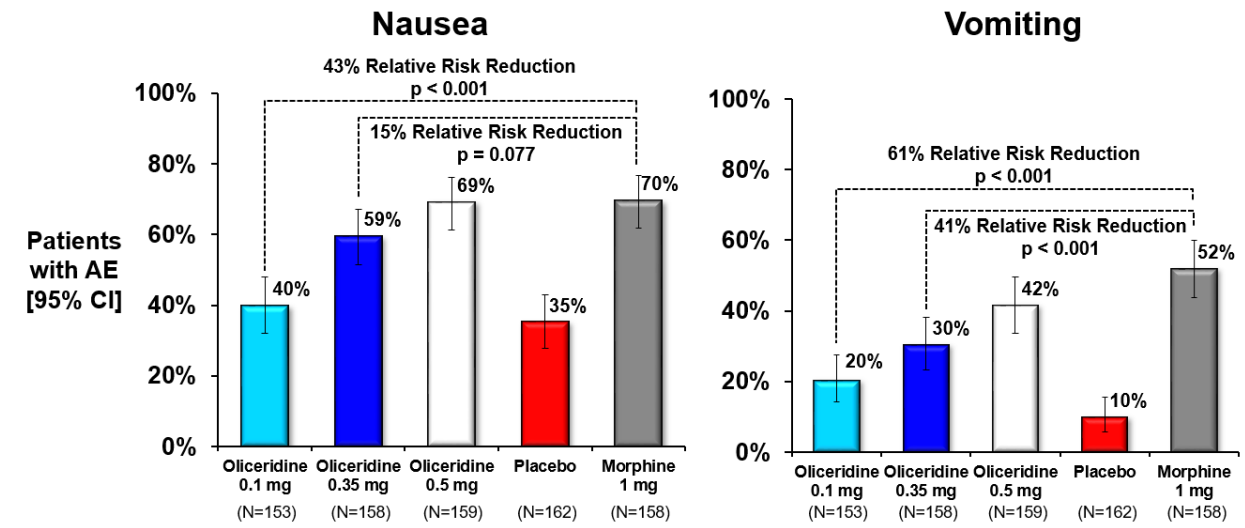


Figure. 10. Postoperative Nausea and Vomiting in Controlled Phase 3 Studies.

Specific Aims

Primary Aims

1. Estimate the proportion of patients having an adjudicated meaningful respiratory compromise with a specified precision of 0.15 using a 95% confidence interval at 24 hours post first study dose. Adapted from PRODIGY,[8] meaningful respiratory compromise will be defined by a collapsed (one or more) composite:
    1) End-tidal PCO_2 ≤ 15 mmHg for ≥3 minutes;
    2) RR ≤ 5 breaths/minute for ≥3 minutes;
    3) SpO_2 ≤ 85% for ≥3 minutes;
    4) Apnea episode lasting >30 seconds;
    5) Any serious respiratory event, defined by:
        - Naloxone administration;
        - Insertion of oral or nasal airways;
        - Non-invasive ventilatory support including for bag and mask ventilation;
        - Rapid Response Team activation;
        - Unplanned ICU transfer;
        - Unplanned intubation;
        - Cardiopulmonary arrest.
2. Evaluate multicenter feasibility of the trial including:
    a. enrollment of an average of 2 patients/week at each participating center;
    b. evaluate protocol compliance and identify obstacles;
    c. complete and accurate data acquisition and submission to the trial coordinating center.

Secondary Aims

1. Estimate cumulative time with saturation <90% .
2. Estimate cumulative time with respiratory rate <8 breaths/minute.

Exploratory Aims

1. Estimate the proportion of patients with complete GI response, defined as no vomiting and no rescue anti-emetic.
2. Estimate the proportion of patients with somnolence and/or sedation over the initial 48 postoperative hours while hospitalized.
3. Estimate the proportion of patients with delirium over the initial 48 hours while hospitalized.
4. Estimate the proportion of patients with primary outcome by surgery type, PRODIGY score, age (≤65 or ≥65 years) and BMI (<35 or ≥35 kg/m^2).
5. Estimate the proportion of patients developing ileus over the initial 48 postoperative hours.

Methods

The trial will be conducted with IRB approval at each participating center and written patient consent, including consent to share data with the trial coordinating center at the Cleveland Clinic. We anticipate enrolling patients at the Cleveland Clinic Main Campus, Cleveland Clinic Fairview Hospital, and Wake Forest University. The Cleveland Clinic IRB approval will include the Main Campus and Fairview Hospital. Each site will enroll 3-6 pilot patients to demonstrate suitable technical accuracy and adequate postoperative ventilatory monitoring. These data will be evaluated by the investigators and only reported to the relevant IRBs if a protocol amendment is indicated.

There will be no restriction on sex, race, or ethnicity; all qualifying patients will be asked to consider the trial. The trial will be registered at ClinicalTrials.gov before the first patient is enrolled. A full statistical analysis plan will be developed before any data are evaluated. Reporting will be consistent with the CONSORT guidelines.

Subjects will provide written informed consent before any protocol-specified procedures or assessments are performed. Screening procedures will be completed within 30 days before arrival for the scheduled surgery (Day -30 to Day -1). Screening activities must be completed between Day -30 and Day -1, and may be completed on more than one day within that timeframe, as clinically necessary. Qualification for the trial will be reconfirmed the morning of surgery before enrollment.

Once patients are enrolled, they will remain in the trial unless they need to be removed for safety reasons or if patients ask to end oliceridine administration and/or Masimo continuous monitoring. Patients who wish to withdraw or modify their approval will be given two options: 1) withdraw completely, with no further experimental drug (oliceridine) or continuous monitoring, or 2) continue oliceridine analgesia (including rescue with other opioids as indicated), but discontinue all or part of the continuous Masimo monitoring. If patients withdraw completely, data obtained before withdrawal will be retained for analysis.

Trial management will include an Executive Committee and a broader Steering Committee. The Steering Committee will advise the Executive Committee and Principal Investigator.

Consenting patients will be **eligible** if they are:

1. ≥18 years old;
2. American Society of Anesthesiologists physical status 1-4;
3. Scheduled for major noncardiac surgery expected to last at least 2 hours;
4. Expected to remain hospitalized at least two postoperative nights;
5. Scheduled for general endotracheal, spinal anesthesia, or the combination;
6. Expected to require substantial opioid analgesia, defined as ≥20 mg morphine equivalents;
7. Expected to have patient-controlled intravenous analgesia.

Patients will be **ineligible** if they:

1. Are demented or otherwise cannot provide valid consent;
2. Have contraindications to oliceridine;
3. Used legal or illegal opioids chronically, defined as >15 mg morphine equivalents for >15 days during the month before consenting by history;
4. Have language, vision, or hearing impairments that may compromise continuous ventilation monitoring;
5. Have planned epidural anesthesia/analgesia;
6. Planned spinal morphine administration;
7. Are designated Do Not Resuscitate, hospice, or receiving end of life therapy;
8. Are expected to require postoperative mechanical ventilation or ICU admission;
9. Are expected to receive intrathecal opioids;
10. Use oxygen at home;
11. Are unwilling or unable to comply fully with study procedures (including not tolerating the capnography cannula);
12. Are known to be pregnant or breastfeeding;
13. Use CPAP at home and plan to use it in the hospital;
14. Have previously participated in the trial.

Protocol

In all cases, good judgment will predominate. Clinicians should always act in their patients' best interests, irrespective of this protocol.

Pre-Operative

Patients may be premedicated with midazolam as needed to treat anxiety. Patients may be given preoperative acetaminophen. Ketamine can be used preoperatively as an anxiolytic, including during insertion of regional blocks.

Intra-Operative

General anesthesia, if planned, will be induced with propofol or etomidate. Anesthesia will be maintained per clinical preference, with propofol and/or a volatile anesthetic. Anesthetic dose, muscle relaxation, and fluid administration will be per clinical routine. Ketamine will not be used unless specifically indicated clinically. Single-shot spinal anesthesia, if clinically indicated, will be induced and maintained per routine except that fentanyl will be the only permitted spinal opioid. Preoperative and intraoperative opioid will be restricted to fentanyl and the oliceridine which will normally be started shortly before or just after anesthetic emergence.

Nausea and vomiting risk will be assessed based on the Apfel score, with one point each assigned for: 1) female sex; 2) non-smoking status; 3) history of motion sickness; and, 4) anticipated use of opioid analgesia (enrollment criterion).[20] Patients with score of 0-2 will be given 4 mg of ondansetron near the end of surgery; patients with higher scores will be given both dexamethasone 4 mg near the beginning of surgery and ondansetron

4 mg near the end of surgery.[21] No other prophylactic anti-emetics will be permitted, including scopolamine patches.

End Of Surgery

Near the end of anesthesia, patients will be given ≤1.5 mg of oliceridine as a bolus. A second ≤1.5 mg bolus can be given if clinically indicated, especially if there is a long period between the initial dose and initiation of PCA dosing.

Post-Operative

Postoperatively, patient-controlled analgesia (PCA) will be started with no background infusion, demand doses of 0.35 mg or 0.5mg, with a 6 minute lock-out. Additional boluses of oliceridine 1-3mg every 1-3 hours can be given as deemed necessary, based on NRS score and clinical assessment of the patient.

If bolus doses of oliceridine and increasing the PCA demand dose to 0.5 mg have not controlled pain (e.g., pain scores consistently exceed 6 points within 2 hours of rescue dose administration, on a 0-10 NRS scale), boluses of fentanyl or hydromorphone can be given for rescue. Local or regional blocks can also be used for rescue if necessary. PCA will continue for at least 48 hours while patients remain hospitalized. PCA can be continued thereafter, but with a conventional opioid. That is, trial drug administration will cease at 48 hours, or hospital discharge if earlier. Thereafter patients can be transitioned to other analgesics including oral or transdermal conventional opioids. Analgesic adjuvants such as acetaminophen can be given per clinical routine.

Use of supplemental oxygen will be permitted, with the amount, delivery mode, and duration being recorded. Postoperatively, patients can be treated as necessary for nausea and/or vomiting.

Measurements

Cognitive function will be evaluated preoperatively with the Mini-Mental State Examination (MMSE) with scores ranging from 0 to 30, with higher scores indicating better function.[22] Anxiety and depression will be evaluated with the Hospital Anxiety and Depression Scale, with scores ranging from 0 to 21 for either anxiety or depression, with higher score indicating more severe symptoms. Scores >7 will be considered thresholds for both anxiety or depression.[23]

Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Elements of the STOP-BANG questionnaire and PRODIGY risk score will be recorded at screening or on the morning of surgery pre-operatively. Cardiopulmonary risks will be recorded, including hypertension requiring treatment, diabetes requiring oral medications or insulin, history of previous myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, current smoking status, and pack-years of smoking history. Cardiovascular and pulmonary medications will be similarly recorded by category, including beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers,

statins, bronchodilators, and inhaled steroids. Chronic opioid use will be characterized as the average in morphine equivalents over the 30 days before surgery.

Baseline laboratory values (within 30 days before surgery) will be recorded on an as-available basis, including albumin, BNP, NT-ProBNP, and FEV1. Results of sleep studies will similarly be recorded. Anesthesia will be characterized as general, neuraxial, or combined. Use of peripheral nerve blocks will also be recorded. Routine anesthetic variables will be recorded including volatile anesthetic partial pressure, fluid type and volume, estimated blood loss, and transfusions. Types of surgery will be characterized as orthopedic, laparoscopic, open abdominal, neurosurgical (including spine), thoracic, urologic, gynecologic, vascular, and other. Timing will be characterized as elective, urgent, or emergent.

Trial drug doses will be recorded during the initial and second 24 postoperative hours including information on PCA interruptions. Each acetaminophen dose will be recorded. Treatments and doses of analgesics given for breakthrough pain will be recorded, along with any other analgesic interventions including regional blocks.

Verbal response pain scores on a 0-10 Likert score (10 = worst) will be recorded every 15 minutes for the first postoperative hour and then every 4 hours per nursing routine. Additionally, pain at rest and while sitting and coughing will be recorded twice daily by investigators during the initial 48 postoperative hours. The Pasero Opioid-induced sedation will be assessed every 15 minutes for the first postoperative hour and then morning and late afternoon or evening daily to evaluate somnolence and sedation.[24] The Opioid-Related Symptom Distress Scale will be used once a day to evaluate the impact of opioid related side effects. Quality-of-recovery-15 will be assessed on the 2nd postoperative morning in person or by phone in patients already discharged. The instrument has been validated for use by phone.[25]

We will use the 3D-CAM which is based on a three-minute questionnaire, and has a sensitivity of 95% (95% CI, 84, 99), and specificity of 94% (CI: 90, 97) compared with formal psychometric evaluation.[26] The test works well in patients with dementia.[26] CAM-ICU, which is also well validated, will be substituted when patients are intubated.[27] Delirium will be assessed by investigators trained in the methods. Any positive CAM test will be considered evidence of delirium which will analyzed dichotomously. Delirium will be assessed morning and evening for 48 hours, starting on the first postoperative morning.

Immediately before assessing delirium, sedation or agitation will be assessed using the Richmond Agitation Sedation Scale (RASS). Scores ranging from –5 (unarousable) to +4 (combative), with 0 indicating alert and calm.[28] For deeply sedated or unarousable patients (RASS –4 or –5), delirium will not be assessed and the patient was recorded as comatose.

Sleep will be assessed with the National Institutes of Health-sponsored Patient-Reported Outcomes Measurement Information System (PROMIS) score for sleep disturbance.[29] PROMIS is a set of person-centered measures that evaluate physical, mental, and social

health in adults and children that are available for use at no cost (https://www.healthmeasures.net/explore-measurement-systems/promis). The PROMIS Sleep Disturbance and Sleep-Related Impairment item banks were developed using rigorous systematic methodology which included literature review, qualitative item review, focus groups, cognitive interviews, and psychometric testing using methods from both classical test theory and item response theory.[29,30] The four-item instrument PROMIS Short Form v1.0 – Sleep Disturbance 4a assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. It is validated for phone use.

Sleep disturbance will be assessed in person preoperatively using the four-item instrument PROMIS Short Form v1.0 – Sleep Disturbance 4a. Sleep will again be assessed on the third postoperative morning in person or by phone if necessary, with the instrument modified to ask about sleep "since surgery" rather than during the standard "previous 7 days."

The final score is represented by the T-score, a standardized score with a mean of 50 and a standard deviation of 10. A T-score of 60 is one SD worse than average. By comparison, a Sleep Disturbance T-score of 40 is one SD better than average. Detailed measure-specific scoring guidance is available at: https://www.healthmeasures.net/explore-measurement-systems/promis.

There is no optimal ward respiratory monitoring system.[31] But the best appears to be the Masimo Radius VSM, and we will use that monitor for the initial 48 postoperative hours (**Fig. 11**, Appendix 1). The monitor will be used in *blinded* mode. Clinicians will therefore not have access to any values — and will therefore make clinical decisions exclusively based on routine monitoring, typically vital sign assessments at 4-6-hour intervals.

Figure 11. Masimo Radius VSM.	 Masimo Radius VSM™ (Photo: Business Wire)

The monitoring system, **Figure** 12, includes:

- Masimo SET Measure-through Motion and Low Perfusion pulse oximetry,[32] including oxygen saturation (SpO_2), pulse rate (PR), perfusion index (Pi), PVi fluid responsiveness, and RRp plethysmographic respiration rate.

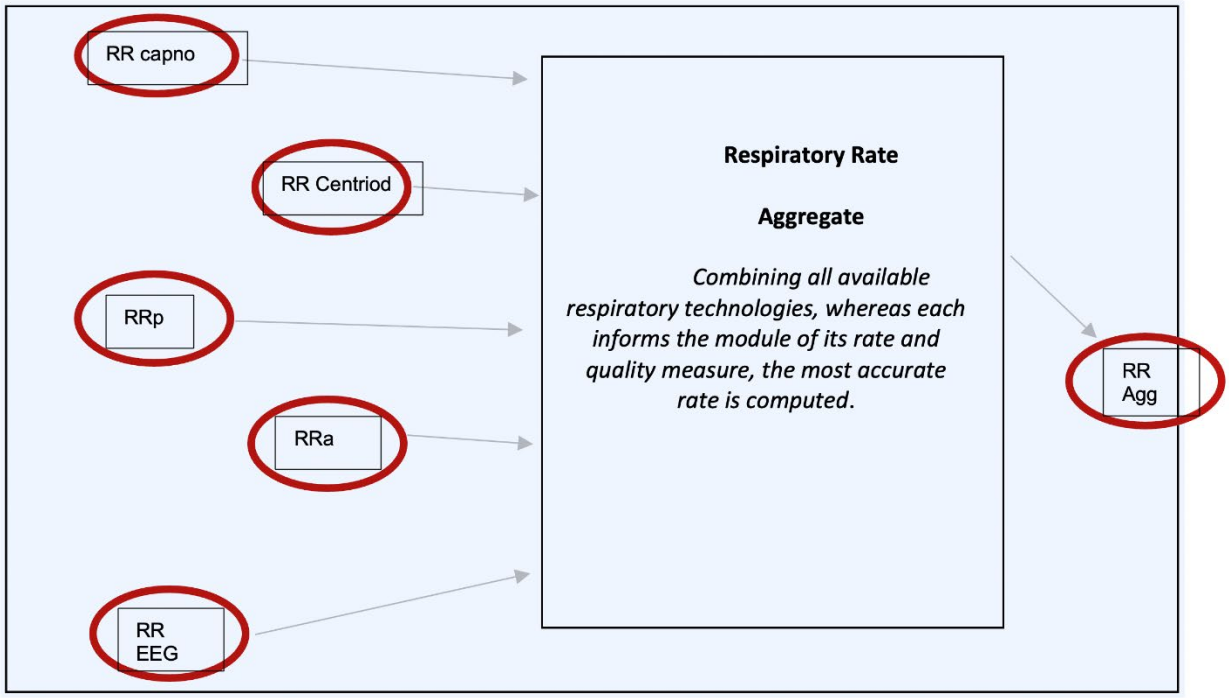
- ECG with heart rate, respiration rate, and advanced lethal arrhythmia detection using 3-lead single-patient-use electrodes offering 6 ECG waveforms: I, II, III, aVR, aVL, and aVF.

- Measure-on-inflation noninvasive blood pressure that features single-patient-use cuffs, customizable scheduling (eliminating the need for periodic manual clinician measurement), and variable inflation speeds; for example, quicker for ambulating patients and slower for resting patients, minimizing the possibility of sleep disruption.

- Continuous body temperature measurements with notifications when clinician-specified temperature thresholds are breached.

- RRa continuous acoustic respiration rate monitoring using rainbow Acoustic Monitoring, which converts the acoustic patterns caused by the patient's airflow into breath cycles to calculate respiration rate and visualize an acoustic respiration waveform.

Figure 12:



Monitoring will continue for 48 hours as tolerated by participating patients. Measurements will be recorded but not available to the responsible clinical teams. These data will be provided to an Adjudication committee. Opioid-related side effects will also be recorded (Appendix 3). Oliceridine-related side effects will be recorded, including QT-interval prolongation, hypotension, seizures, and headaches.

Data analysis

Primary, secondary, and exploratory outcomes will be analyzed on a modified intent-to-treat basis. Specifically, we will include all treated patients who have surgery, even if the operation is changed to one that would not otherwise qualify for the trial.

Respiratory compromise will be adjudicated centrally using available records using the definition in Specific Aims. Two physicians will independently evaluate candidate events. Divergences will be resolved by consensus when possible. If necessary, a senior clinician will determine whether events meet the criteria for respiratory compromise.

A full statistical analysis plan will be developed before data are accessed for analysis. We plan to have interim analyses after 50 and 125 patients are accrued. Because VOLITION is a single-group pilot study, analyses will be purely descriptive and

interim results will guide discussions about future trial designs. All analyses will be conducted using SAS statistical software version 9.4, Cary, NC.

Sample size considerations

Table 2 shows the precision obtained based on sample size and proportion of patients with the primary endpoint of respiratory compromise based on the Masimo Radius VDM system.

Table 2: Width of 95% CI for primary outcome by sample size and underlying proportion						
	N=180		N=200		N=220	
Proportion	90	180	100	200	110	220
0.10	0.14	0.09	0.13	0.09	0.12	0.08
0.20	0.18	0.12	0.16	0.12	0.16	0.11
0.30	0.20	0.14	0.19	0.13	0.18	0.12
0.40	0.21	0.15	0.20	0.14	0.19	0.13

Based on literature,[7,8] the range of proportion of patients who have a respiratory depression event is expected to be between 10% and 40% with a precision expectation of 0.15. A sample size of 200 is sufficient to meet the primary aims of this study. There will be no additional adjustments for early withdraw.

Data management

Trial data will be entered at each site into a custom secure Redcap database that will be maintained at the coordinating center in Cleveland. Redcap includes an audit trail which identifies all access and changes. The database is maintained on secure Cleveland Clinic servers and backed up to remote sites nightly. The system will record who accessed the system and when it was accessed. The database will include appropriate range checks and track all changes. Waveform-level will be retrieved from Masimo devices and uploaded to Redcap.

Each site will have separate designated investigator teams. Each investigator will personally log into Redcap, and only have access to appropriate information. Investigators will enter all postoperative data including all trial outcomes.

Fairview Hospital will be visited monthly by Outcomes Research regulatory coordinators, and a suitable number of randomly selected trial patients audited. Per routine, audits will confirm that informed consent was obtained and check that values recorded in Redcap match case report forms and source documents (primarily medical records). Submitted data will also be statistically audited using the method of Carlisle[33] and similar approaches.

Limitations

As a single-group cohort, the proposed pilot study will estimate the incidence of respiratory complications in patients given oliceridine analgesia. However, it will not provide any indication of the relative respiratory effects of oliceridine and conventional opioids. The study is nonetheless important because the Masimo Radius VDM is not yet

FDA cleared, although components of the system are. It is thus non-obvious what the incidence of respiratory compromise will be, as detected by the Masimo Radius.

The proposed study will be open-label and thus potentially subject to bias. However, our primary outcome is objective and unlikely to be influenced. As with any pilot study, power will be limited. It will, though, be sufficient to estimate the proportion of patients with respiratory events to within ±0.15 which will guide the sample-size estimate for a future full trial.

Human Subjects Protection

In all cases, good judgement will predominate. Clinicians should always act in their patients' best interests, irrespective of the protocol.

The trial will be conducted with IRB approval at each participating center and written patient consent, including consent to share data with the trial coordinating center at the Cleveland Clinic. Protected health information will be retained locally. Only de-identified data will be shared.

Patients will be paid $3/hour of successful monitoring time, to a maximum of 48 postoperative hours. Our intent is to pay patients for monitoring time, even if unsuccessful because of technical difficulties, but not for periods when they electively remove or disable the monitors. If the only monitor electively removed is the nasal cannula from the Masimo monitor, patients will continue to be paid. Payment will be made by check within 8 weeks after discharge.

Oliceridine is an FDA-approved opioid analgesic. It will be used for an approved indication, via an approved route, and we will not exceed the approved daily dose. Oliceridine is the first in a new class of G-protein biased opioids that are potentially comparably analgesic, but less toxic than conventional opioids. It will be used in approved doses and for approved indications. Sparse available information suggests that oliceridine produces less respiratory toxicity, less sedation, and less nausea and vomiting than conventional opioids. In general, the toxicities of oliceridine are similar to those of other opioids.

Various questionnaires will be used to assess sedation, quality of recovery, and delirium. All are short, and none requests sensitive information. Participants will, of course, be free to decline any that bothers them.

The Masimo Radius respiratory monitor consists of a pulse oximeter, an end-tidal PCO2 monitor, an acoustic breath monitor, an accelerometer-based respiratory monitor, a plethesmography-based ventilation monitor, and an impedance respiratory monitor. Output from these monitors is combined by Radius software which evaluates the reliability of each input (based on signal characteristics), thereby estimating the true ventilation rate on the basis of available evidence. The individual components are FDA cleared, but the

Radius software is not. However, the monitor will be used only in blinded recording mode. Output from Radius devices and software will not be available to guide clinical decisions, and therefore will not influence clinical care. Use of the Radius monitor will be somewhat annoying to patients (who of course can discontinue monitoring or parts of the monitoring system any time), but will not alter their clinical care.

Potential drug interactions

There are three known potential drug interactions with oliceridine, listed below along with the relevant mitigation strategy for each.

1. Moderate and Strong CYP2D6 and CYP3A4 Inhibitors: Patients may require less frequent dosing. Monitor closely and administer subsequent doses based on severity of pain and patient response. **Strategy**: All patients will be hospitalized and thus monitored reasonably well. Dosing, after the initial bolus, will be per PCA which automatically titrates dose to need.
2. Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue oliceridine if serotonin syndrome is suspected. **Strategy**: We will discontinue oliceridine if the syndrome is suspected.
3. Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with oliceridine because they may reduce analgesic effect of oliceridine or precipitate withdrawal symptoms. **Strategy**: Per protocol, patients will not be given mixed agonist/antagonist and partial agonist opioid analgesics.

Adverse Events

An AE is any untoward medical occurrence in a study subject which is temporally associated with the use of a medicinal product, regardless of its potential relationship to the medicinal product. An AE, therefore, can be any unfavorable or unintended sign, including a clinically-significant abnormal laboratory finding, symptom, or disease temporally associated with the use of the study medication, whether or not it is considered to be study medication related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study medication.

Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study medication administration even though it may have been present prior to the start of the study.
- Signs, symptoms of a drug interaction.
- Signs, symptoms of a suspected overdose of either study medication or a concurrent medication.
- A laboratory abnormality occurring after the start of the study (i.e., after Screening) that results in subject withdrawal from the study, medical treatment, or further follow-up.

Abnormal laboratory values obtained during Screening that preclude a subject from entering the study are not considered AEs but will be recorded. AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e.,

invasive procedures, modification of subject's previous therapeutic regimen). Normal sequelae of venipuncture, such as bruising or soreness, will not be recorded as AEs unless they are of greater severity and/or intensity than would be expected. Investigators will use their clinical judgment in determining whether the symptoms or signs are of greater severity and/or intensity than would be expected. A medical intervention to address an AE is an 'action taken' and not an AE itself.

Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

(a) Results in death.

(b) Is immediately life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(c) Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out -patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered 'serious'.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE, nor is prolongation of hospitalization for non-medically-driven circumstances (e.g., transportation issues).

(d) Results in persistent or significant disability or incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) Is a congenital anomaly/birth defect.

(f) Is an important medical event.

NOTE: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note that the terms 'serious' and 'severe' ARE NOT synonymous. The term 'severe' is often used to describe the intensity (severity) of a specific event (as in, 'mild', 'moderate', or 'severe' myocardial infarction); the event itself, however, may be

of relatively minor medical significance (such as a 'severe' headache). This is NOT the same as 'serious', which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A 'severe' AE does not necessarily need to be considered 'serious'. For example, persistent nausea of several hours' duration may be considered 'severe' nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered 'mild' but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

NOTE: Requires expedited reporting to the Health Authorities.

Evaluating Adverse Events and Serious Adverse Events

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the study medication:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the study medication.

Severity Rating

Each AE will be classified according to the following criteria:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or perform usual activity

An AE that is assessed as 'severe' should not be confused with a SAE. An event is defined as 'serious' when it meets one of the predefined outcomes as described below. When changes in the intensity of an AE occur more frequently than

once a day, the maximum intensity for the experience should be noted. If the intensity category changes over several days, those changes should be recorded separately (with distinct onset dates).

Relationship to Investigational Product

For AEs and SAEs, the relationship to study treatment is to be assessed according to the following definitions:

Not Related There is no reasonable association between the study treatment and the suspected event.

Unlikely Related It is doubtful that there is an association between the study treatment and the suspected event. The event could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Possibly Related The suspected AE may or may not follow a reasonable temporal sequence from study treatment administration. The event could have been produced or mimicked by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.

Probably Related The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the subject's clinical state.

When assessing the relationship to the study medication, the following criteria will be considered:

- Positive rechallenge
- Positive dechallenge (resolution upon stopping the suspect study medication, in absence of other intervention or treatment)
- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

Reporting Adverse Events

Adverse Events

Events occurring from the time of signed informed consent to just before the first dose of study medication will be considered as medical history. A baseline AE assessment will occur just before the first dose of study medication. All AEs between the baseline AE assessment to the end of the Follow-Up Phase, inclusive, will be recorded in source and EDC, whether or not considered study medication related. All AEs that are potentially related to study medication will be followed until resolution or database lock, whichever occurs first. Additionally, the sign, symptom, or disease present before the baseline AE assessment are only considered to be AEs if they worsen after

the first dose of study medication. Any AEs already documented at a previous assessment and designated as 'ongoing' should be reviewed at subsequent visits, as necessary. If these have resolved, this should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

The investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (e.g., "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described above. The investigator will be responsible for evaluation of all adverse events and completing the actions and safety reporting according to FDA and IRB requirements, and providing both aggregate AE reports to Trevena on a quarterly basis, along with copies of any IRB-mandated reports.

Serious Adverse Events

Each adverse event (AE) will be assessed by the investigator and/or medical monitor to determine whether it meets seriousness criteria. If the event is considered serious (SAE) it must be further assessed to determine if it is unexpected and possibly/probably product related. If serious, unexpected, and product related, the investigator must promptly report this event to the FDA within 15 days, and notify Trevena, and the IRB in accordance with their reporting and timeline requirements. Follow up reports should also be provided to the FDA and IRB within specified timeframes with a copy to Trevena,

All other SAEs occurring from the time of signed informed consent to the last Follow-Up Phase contact will be recorded in source/ EDC; reported via the SAE form and included in quarterly safety reports to Trevena as well as the annual IRB safety summary. SAE reports should include the following information:

- Event
- Serious criteria
- Study code
- Subject number, initials, and date of birth
- Study medication
- Reporter name and contact information

Each SAE should be followed up until resolution or stabilization and for reported deaths, the investigator should supply the IRB and Trevena with any additional requested information (e.g., autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. The investigator will be responsible for determining and, in turn, reporting SAEs to Trevena and regulatory authorities according to the applicable regulatory and IRB requirements.

During both business and non-business hours, the telephone numbers listed should be used if discussion with the medical monitor is required:

Primary Medical Monitor and 24-hour Emergency Contact

Kurt Ruetzler, M.D.
Staff Anesthesiologist
Department of General Anesthesiology and Outcomes Research
Cleveland Clinic
9500 Euclid Ave - E3
Cleveland, OH 44195
Tel: 216 407-4108
email: ruetzlk@ccf.org

Backup Medical Reviewer

Alparslan Turan, M.D.
Professor and Vice-chair
Department of Outcomes Research
Cleveland Clinic
9500 Euclid Ave - P77
Cleveland, OH 44195
Tel: 216-445-9857
Mobile: 216-217-2312
email: turana@ccf.org

Email for SAE reporting: Send to both SAETRV130@wcgclinical.com and Drugsafety@trevena.com.

Change log

1. Post-Oberative section updated dosing language of oliceridine bolus. Date: 4/5/2022.
2. Added further language around patient withdrawal scenarios. Clarified medications allowed pre surgery. Provided allowance of a second bolus of study drug if clinically necessary immediately post operative. Input new language about interim analysis allowance, timing, and purpose. Added in further language clarifying that patients can discontinue the nasal cannula measurement of the Masimo device without concern for downstream data or status in the trial.
   Reason: Being a pilot, we are learning that some patients elect to withdraw altogether from the trial in the post operative period, whereas some wish to just remove the Masimo technological assessments; language was added to explain these scenarios and what would be done in each (including but not limited to patient stipend, and logistics around just nasal cannula removal). Ketamine is allowed in the pre-operative setting, and language was added to clarify how and why. A second oliceridine bolus could be necessary clinically, depending on the patient's needs and clinical judgment. Interim analysis, upon further discussion, is desired to help guide future trials and two interim analyses prior to final study report would be

ideal in what could be gleaned from the data and how to guide us moving forward. Date: 03/08/22.

3. Removed other language in protocol section referring to previously removed language/exclusion criteria about gabapentinoids and analgesic adjuvants. Removed likeability questionnaire.
   Reason: gabapentinoid language removed for consistency with previous protocol version. Likeability scale removed due to lack of applicability in this population. Date: 02/01/22.
4. Restriction on gabapentinoids and analgesic adjuvants eliminated. Reason: Restricted enrollment with little value since gabapentinoids are probably ineffective in the perioperative period. Date: 12/20/21.
5. Exclusion changed to CPAP use at home *and planned use in the hospital*. Reason: the restriction is only relevant if CPAP used in-hospital. Date: 12/20/21.

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Schedule of Events

Assessment	Screening (Day-30 to Day -1)	Day of Surgery (Day 0) Pre-Op	Day of Surgery (Day 0) Post-Op	Post-Operative Day 1	Post-Operative Day 2	Post-Operative Day 3
Informed Consent[1]	X					
Demographics[2]	X					
Medical History	X	X	X			
Current Medications	X	X				
Chronic Opioid Use (30 days before surgery)	X					
Baseline Laboratory Values	X	X				
STOP-Bang Questionnaire[2, 16]	X	X				
PRODIGY Risk Score[2, 16]	X	X				
PROMIS Score[3]		X				X
Apfel Score[4]	X					
Assess/Confirm Eligibility	←	———	→			
Hospital Anxiety and Depression Scale[5]		X				
Mini-Mental State Examination[6]		X				
Oliceridine Administration[7]			← ——— →			
Verbal Response Pain Scores[8]			← ——— →			
Pain at Rest and while Sitting and Coughing[9]			← ——— →			
Pasero Opioid-Induced Sedation Scale[10]			X	X	X	
Opioid-Related Symptom Distress Scale[11]				X	X	
Quality-of-Recovery-15 (QoR-15 Questionnaire)[12]					X	

Richmond Agitation Sedation Scale (RASS)[13]				X	X	
3D-CAM/CAM-ICU (Delirium Assessment)[14]				X	X	X
Ward Respiratory Monitoring using Masimo Radius VSM[15]			←	—	→	
Adverse Events	←	—	—	—	—	→

[1]Patients will provide written informed consent before any protocol-specified procedures or assessments are performed. Screening procedures will be completed within 30 days before the day of surgery

[2]Baseline demographic and morphometric characteristics will be recorded, including height, weight, and sex. Elements of the STOP-BANG questionnaire and PRODIGY risk score will be recorded.

[3] Sleep disturbance will be assessed in person preoperatively using the four-item instrument PROMIS Short Form v1.0 – Sleep Disturbance 4a. Sleep will again be assessed on the third postoperative morning in person or by phone if necessary, with the instrument modified to ask about sleep "since surgery" rather than during the standard "previous 7 days."

[4]Nausea and vomiting risk will be assessed based on the Apfel score, with one point each assigned for: 1) female sex; 2) non-smoking status; 3) history of motion sickness; and, 4) anticipated use of opioid analgesia (enrollment criterion). Patients with score of 0-2 will be given 4 mg of ondansetron near the end of surgery; patients with higher scores will be given both dexamethasone 4 mg near the beginning of surgery and ondansetron 4 mg near the end of surgery. No other prophylactic anti-emetics will be permitted, including scopolamine patches.

[5]Anxiety and depression will be evaluated with the Hospital Anxiety and Depression Scale, with scores ranging from 0 to 21 for either anxiety or depression, with higher score indicating more severe symptoms. Scores >7 will be considered thresholds for both anxiety or depression.

[6]Cognitive function will be evaluated preoperatively with the Mini-Mental State Examination (MMSE) with scores ranging from 0 to 30, with higher scores indicating better function.

[7] Postoperatively, patient-controlled analgesia (PCA) will be started with no background infusion, demand doses of 0.35 mg or 0.5mg, with a 6 minute lock-out. Additional boluses of oliceridine 1-3mg every 1-3 hours can be given as deemed necessary, based on NRS score and clinical assessment of the patient.

[8]Verbal response pain scores on a 0-10 Likert score (10 = worst) will be recorded every 15 minutes for the first postoperative hour and then every 4 hours per nursing routine [9]Pain at rest and while sitting and coughing will be recorded twice daily by blinded investigators during the initial 48 postoperative hours.

[10]The Pasero Opioid-induced sedation will be assessed every 15 minutes for the first postoperative hour and then morning and late afternoon or evening daily to evaluate somnolence and sedation

[11]The Opioid-Related Symptom Distress Scale will be used once a day to evaluate the impact of opioid related side effects.

[12]QoR-15 will be assessed on the 2nd postoperative morning in person or by phone in patients already discharged.

[13]Immediately before assessing delirium, sedation or agitation will be assessed using the RASS (NOTE: For deeply sedated or unarousable patients (RASS –4 or –5), delirium will not be assessed, and the patient will be recorded as comatose.

[14]Delirium will be assessed morning and evening for 48 hours, starting on the first postoperative morning (NOTE: this should be assessed after the RASS).

[15]Patients will be monitored for the initial 48 postoperative hours.

[16]Elements of the STOP-BANG questionnaire and PRODIGY risk score will be recorded at screening or on the morning of surgery pre-operatively

Appendix 1, Masimo Radius Technical Details

[Separate document.]

Appendix 2, Sedation Scoring

ASA Continuum of Depth of Sedation	Modified Ramsay	Modified Ramsay	MOAA/S
Anxiolysis: Normal response to verbal stimulation. Cognitive function and coordination may be impaired. Airway, ventilation, and cardiovascular function unaffected.	1 = Anxious	1 = Anxious	5 = Responsive and alert
	2 = Awake, tranquil	2 = Awake, tranquil	
Moderate Sedation/Analgesia: (Formerly termed "conscious sedation") Purposeful response to verbal commands or light tactile stimulation. No airway intervention is required. Adequate spontaneous ventilation. Cardiovascular function is usually maintained.	3 = Drowsy, responds easily to verbal commands	3 = Drowsy, responds easily and purposefully to verbal commands	4 = Lethargic, but responsive to normal verbal command
	4 = Asleep, brisk response to tactile or loud auditory stimulus	4 = Asleep, brisk purposeful response to tactile or loud auditory stimulus	3 = Responsive to loud verbal command
Deep Sedation: Not easily aroused. Purposeful response following repeated or painful stimulation. Airway intervention may be required. Spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. Note: Reflex withdrawal from painful stimuli is NOT considered purposeful.	5 = Asleep, minimal response to tactile or loud auditory stimulus	5 = Asleep, minimal response to repeated painful or loud auditory stimulus. Response is still purposeful and not reflex withdrawal	2 = Responsive to shaking only

Appendix 3, Opioid-related Side Effects

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs considered to be solely due to the use of opioid medication. Opioid-related adverse drug events will be measured using standard of care bedside monitoring, including best clinical judgment of the bedside nurse/clinician.

Any opioid-related adverse drug event involving impaired respiratory function. Respiratory opioid-related adverse drug events will be measured using standard bedside monitoring, including best clinical judgment of the bedside nurse/clinician. Anticipated respiratory opioid-related adverse drug events include:

1. Respiratory opioid-related adverse drug events;
2. Narcotic overdoses that require opioid reversal;
   Partial airway obstruction that require an neuromuscular blocking agent antagonist;
3. Respiratory failure that requires mechanical ventilation;
4. Upper airway obstruction requiring airway support measures (oral or nasal);
5. Respiratory insufficiency or failure requiring transfer to the ICU;
6. Cardiopulmonary arrest or death due to respiratory or pulmonary causes;
7. Respiratory insufficiency that requires non-invasive positive pressure ventilation such as Ambu bag mask assisted ventilation.