ARTEMIS, A Real-World Evidence Trial Examining the Use of Oliceridine, a Biased Agonist at the μ(Mu) Receptor, in Patients Requiring Post-Surgical Pain Control

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INTRODUCTION

- Conventional opioid analgesics, such as morphine, fentanyl, and hydromorphone, are mainstays of acute pain management; however, their use is accompanied by well-known opioid-related adverse events (ORAEs) including nausea, vomiting, and central nervous system effects
- Oliceridine is a G protein-biased μ–opioid receptor agonist that has demonstrated analgesic efficacy superior to placebo and comparable to morphine, with favorable outcomes related to ORAEs[1-5]
- In 2020 OLINVYK® (oliceridine) injection, Trevena, Inc., was approved for use in adults in the management of acute pain severe enough to require an intravenous (IV) opioid analgesic and for whom alternative treatments are inadequate[6]
- Nonclinical findings support the hypothesis that oliceridine substantially reduces activation of the β-arrestin pathway, which contributes to ORAEs including respiratory depression and GI dysfunction[1]
- Economic analyses suggest that the use of oliceridine has a positive economic impact in the hospital environment[7,8]
- We further hypothesized that, in its real-world use, oliceridine-treated patients may show less healthcare utilization and ORAEs than patients treated with other opioids

OBJECTIVE

- To measure the real-world effectiveness of use of IV oliceridine on patient and hospitalization endpoints

METHODS

- The ARTEMIS trial is a multi-site, non-interventional, observational, post-operative, electronic medical record (EMR) analysis
  - Comparing use of IV oliceridine among post-surgical patients in an open-label study with a matched population of patients who underwent similar surgical procedures but who were treated with other IV opioids, at the same institution and during the same general time period
- Here, we report on results from a single site (Wake Forest Baptist Health/WFBH) in this non-randomized, controlled, quasi-experimental post-operative study
- EMR extracts identifying a control-treated cohort (receiving either IV morphine, hydromorphone, or fentanyl) for post-surgical pain control was propensity score-matched to an IV oliceridine-treated cohort based on:
  - Age, race, sex, American Society of Anesthesiologists (ASA) physical status, anesthesia time, insurance type, type of surgery, and Charlson Comorbidity Index (CCI)
- Patients were evaluated on differences in hospital length of stay (LOS) and incidence of select ORAEs
- In a second phase, numerical pain ratings and total opioid consumption were compared between groups
  - Hospital pain ratings were based on a 10-point numerical rating scale (1 = no pain to 10 = worst possible pain)
    - Averaged per patient and per group for the first 24 hours; cumulative for 48 hours
  - Total opioid consumption was normalized to morphine milligram equivalents (MMEs)
    - Calculated from date & time stamped entry to post-anesthesia care unit (PACU) for first 24 hours; cumulative through 48 hours

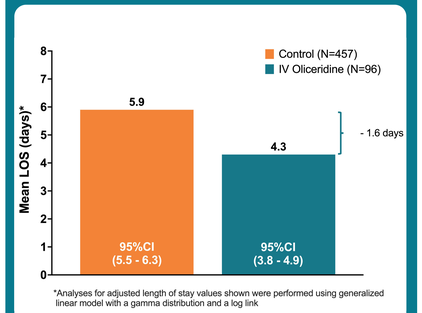
RESULTS

ARTEMIS Demographics and Clinical Features

Variable Name	Oliceridine (N=96)	Control (N=457)	P-value
Age (yrs)			
Mean (SD)	58.9 (15.6)	60.4 (14.5)	.3821
Male Sex			
n (%)	40 (42%)	186 (41%)	.8610
Race, n (%)			.9200
Black	9 (10%)	40 (9%)	
White	80 (83%)	388 (85%)	
Other	7 (7%)	29 (6%)	
Insurance Type, n (%)			.8592
Medicare	39 (41%)	200 (44%)	
Medicaid	39 (41%)	184 (40%)	
Uninsured	2 (2%)	11 (2%)	
Other insurance	16 (16%)	62 (14%)	
Surgery Type, n (%)			.9170
Abdominal	70 (73%)	331 (72%)	
Gynecologic	19 (20%)	87 (19%)	
Neurosurgery	7 (7%)	39 (9%)	
ASA Score			
Mean (SD)	2.9 (0.6)	2.9 (0.6)	.6565
Duration of Surgery (hrs) [Anesthesia time]			
Mean (SD)	4.5 (2.0)	4.6 (2.0)	.7427
Charlson Comorbidity Score			
Mean (SD)	2.9 (3.3)	2.9 (3.2)	.9774

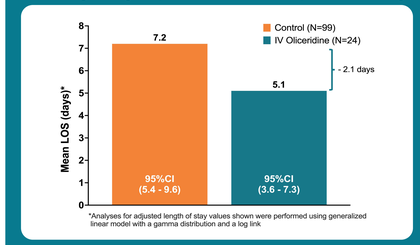
- The propensity score-matched sample included 96 patients treated with IV oliceridine and 457 control patients treated with another IV opioid
- There were no significant differences in demographics, anesthesia time, CCI, or ASA between the two groups

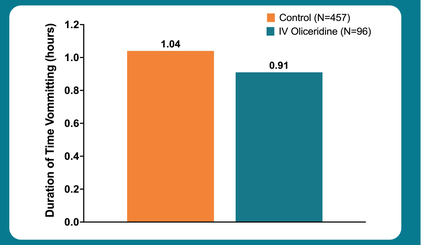
Hospital LOS: Overall Population



- Overall hospital LOS was 1.6 days shorter among oliceridine-treated patients compared with control-treated patients (P<0.0001)
- There was no statistically significant difference in the average duration of time in the PACU

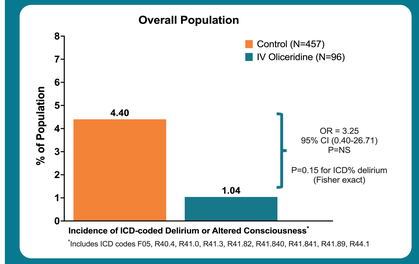
Vomiting Subgroup: LOS and Time Spent Vomiting

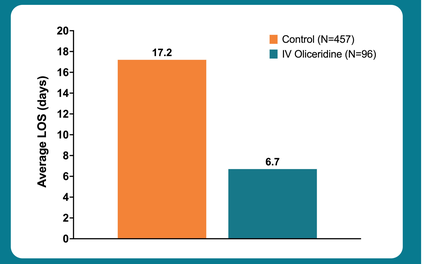




- There was no difference in the incidence of vomiting between the IV oliceridine-treated and other opioid-treated groups (P=0.4748)
- For patients experiencing vomiting, and after adjustment using the same covariates used in matching, overall hospital LOS was significantly reduced among IV oliceridine-treated patients
- IV oliceridine-treated patients had a slightly reduced (NS) average duration of vomiting and a lower variability in the duration of vomiting (P=0.0128)
- There was a slightly reduced average duration of time vomiting (in hours) among IV oliceridine-treated patients (0.91, SD:0.83) compared to other opioid-treated patients (1.04, SD:1.20), though this difference was not statistically significant (P=0.8703)

ICD-coded Delirium Subgroup: Incidence and LOS





- The adjusted odds of a patient in the control group having a diagnosis of delirium or altered consciousness is 3.25 times greater compared with the oliceridine group though this difference was not statistically significant

Numerical Pain Ratings and Total Opioid Consumption: Overall Population

Variable Name	Oliceridine (N=96) Mean (95% CI)	Control (N=457) Mean (95% CI)	Difference	P-value
Mean 24-Hour Pain Score[a]	3.80 (3.40-4.20)	4.32 (4.12-4.52)	-0.52	0.0285
Mean 48-Hour Pain Score[a]	3.58 (3.22-3.93)	4.10 (3.92-4.28)	-0.52	0.0097
Mean 24-Hour MME* (of those taking any)[b]	22.53 (18.39-27.61)	45.56 (40.27-51.30)	-22.93	<0.0001
Mean 48-Hour MME (of those taking any)[c]	27.43 (22.11-34.03)	55.38 (48.76-62.90)	-27.95	<0.0001

*MME = morphine milligram equivalent [5 mg IV morphine = 50 mcg fentanyl (IV or transdermal) = 0.75 mg hydromorphone = 1 mg IV oliceridine]
[a]Statistical analyses for pain values shown were performed using generalized linear model with a normal distribution and an identity link; the data were adjusted for age
[b]Statistical analyses for MMEs values shown were performed using generalized linear model with a gamma distribution and a log link; the data were adjusted for anesthesia time and Charlson score.
[c]Statistical analyses for MMEs values shown were performed using generalized linear model with a gamma distribution and a log link; the data were adjusted for anesthesia time, age, and Charlson score.

- Mean 24- and 48-hour pain scores were significantly lower in the oliceridine group compared to control
- Patients in the control group required twice as much opioids as those in the oliceridine group
- There were 7 (1.53%) naloxone reversals for respiratory depression in the control group and 0 (0%) in the oliceridine group (P=0.61, NS)

CONCLUSIONS

- This real-world EMR analysis demonstrated that use of IV oliceridine compared with other conventional IV opioids for control of acute post-surgical pain can result in a significant reduction in hospital LOS in the overall population as well as subpopulations experiencing ORAEs such as vomiting and delirium
- Oliceridine use also resulted in better pain control and lower total opioid consumption
- Although many variables affect hospital LOS, adequate pain control, decreased opioid consumption and potentially less severe and/or lower incidence of ORAEs in the oliceridine group may contribute to the observed reduction in LOS
- Further analyses are ongoing to assess healthcare resource utilization and costs among these patients

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