Introduction and Overview

Oliceridine
Anesthetic and Analgesic Drug Products
Advisory Committee (AADPAC) Meeting
October 11, 2018

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Introduction of FDA Presentations

- **Introduction and Overview**
  - Elizabeth Kilgore, MD
    - Clinical Reviewer
- **Abuse Potential of Oliceridine**
  - Katherine Bonson, PhD
    - Controlled Substance Staff Reviewer
- **Review of Efficacy**
  - James Travis, PhD
    - Statistical Reviewer
- **Safety Assessment and Benefit/Risk Considerations**
  - Elizabeth Kilgore, MD

Background

- **Indication:** Management of moderate-to-severe acute pain in adult patients for whom an IV opioid is warranted
- **Class:** New molecular entity (NME) opioid
  - Mechanism of Action: G protein-biased ligand that binds to the μ-opioid receptor with less β-arrestin recruitment
- **Dosing Considerations for Advisory Committee:**
  - During the review cycle, Trevena informed the Agency that they are only seeking approval of the oliceridine 0.1 mg and 0.35 mg patient-controlled analgesia (PCA) doses, and not the 0.5 mg dose.
  - However, the Agency considered the efficacy and safety of all three oliceridine dose strengths evaluated in the Phase 3 studies.

Overview of Applicant's Clinical Program

Total 17 Clinical Studies

- 11 Phase 1 studies
- 3 Phase 2 studies
- **3 Phase 3 studies**
  - 2 double-blind, placebo- and active-controlled studies
    - CP130-3001 (3001; post-bunionectomy) and CP130-3002 (3002; post-abdominoplasty)
  - 1 open-label study
    - CP130-3003 (3003; surgical and medical patients)

Select Regulatory History

- 2/19/16: Breakthrough Therapy Designation granted
  - Primarily based on the suggestion of better safety of some opioid-related safety parameters in Phase 2 studies
- 2016-2017: Meetings and Agency Advice
  - Requirements for comparative safety claims were discussed
  - Agency informed the Applicant that their proposed respiratory safety endpoint was not acceptable
  - The NDA was submitted November 2017

Topics for Advisory Committee Consideration

- Efficacy of oliceridine for adults with acute pain
- Safety findings:
  - Safety database
  - Hepatic safety
  - Respiratory safety
  - QT prolongation
- Overall benefit/risk of oliceridine for adults with acute pain

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Abuse Potential of Oliceridine

FDA Anesthetic and Analgesic
Drug Products Advisory Committee Meeting

October 11, 2018

Katherine Bonson, PhD
Pharmacologist
Controlled Substance Staff (CSS)
Office of the Center Director
CDER, FDA

Assessing the Abuse Potential of Oliceridine

- For regulatory purposes, evaluation of a drug's abuse potential is considered to be a safety consideration.
- Under the FDA guidance for industry *Assessment of the Abuse Potential of Drugs* (2017), all CNS-active drugs need to undergo an abuse potential evaluation during drug development.
- Oliceridine is a mu opioid agonist that is proposed for the treatment of acute pain. Thus, it was necessary to conduct an abuse potential assessment for oliceridine.
- During drug development, CSS provided feedback to the Sponsor regarding which abuse-related studies in animals and humans would be required, as well as feedback on their appropriate design.

Applicant's Abuse-Related Assessment

- Receptor binding (where drug acts neurochemically)
- Second messenger studies (intracellular functioning)
- Behavioral studies (using animal doses that produce plasma levels equivalent to or greater than human therapeutic plasma levels):
  - General behavior
  - Drug discrimination (similar sensations to a known drug of abuse)
  - Self-administration (rewarding properties producing reinforcement)
- Clinical study:
  - Human abuse potential (HAP) study

Receptor Binding Studies

- Oliceridine has high affinity for mu opioid receptors, similar to that of other opioids with abuse potential
- No significant affinity of oliceridine for other abuse-related sites:
  - opioid (kappa or delta)
  - GABA/ benzodiazepine
  - dopamine (D_1 or D_2)
  - serotonin (5HT1A, 1B, 2A, 3, 5A, 6, or 7)
  - cannabinoid
  - NMDA/glutamate
  - ion channels (calcium, potassium, sodium, or chloride)
  - monoamine transporters (dopamine or norepinephrine)

Second Messenger Systems

- In classic pharmacology, the binding of an agonist to a particular receptor leads to activation of a single second messenger system to amplify the response.
- However, investigations have shown that there is often more than one intracellular signaling pathway associated with a receptor, and that each of these mechanisms may be responsible for different physiological or behavioral effects.
- Agonists will typically activate all of these second messenger systems after binding to the receptor, but some drugs will preferentially activate only one of them.
- This is called biased agonism.

Mu Opioid Signaling Pathways

- For the mu opioid receptor, there are two main signaling cascades: the G-protein pathway and the beta-arrestin pathway.
- The G-protein signaling pathway is hypothesized to be responsible for opioid-induced analgesia.
- The beta-arrestin signaling pathway is hypothesized to be responsible for opioid-induced respiratory depression and rewarding effects.

Evidence that Oliceridine is a Biased Agonist

- *In vitro* functional studies were conducted in human embryonic kidney (HEK-293) cells expressing recombinant human mu opioid receptors.
- In an assay of G-protein activation, oliceridine inhibited forskolin-stimulated cAMP accumulation. This shows that oliceridine activated the G-protein pathway.
- In an assay of beta-arrestin activation, oliceridine did not produce a measurable formation of an active beta-galactosidase enzyme. This shows that oliceridine did not recruit beta-arrestin.
- In contrast, the mu opioid agonists fentanyl, hydromorphone and morphine each activated both G-protein and beta-arrestin pathways.

The Ideal Opioid Analgesic

- The ideal opioid for therapeutic purposes would produce analgesia without the risk of abuse potential and overdose.
- This has been a research and drug development goal for over a century, but to date, all opioids that produce clinically-relevant analgesia can also get people “high” when the dose is increased enough -- and can produce respiratory depression leading to death.
- Thus, mu opioids that function as biased agonists -- by acting only on G-protein and failing to recruit beta-arrestin -- would appear to be desirable as pharmaceutical drugs.

Mu Opioid Biased Agonists

- Numerous candidate compounds that act as mu opioid agonists, but have reduced recruitment of beta-arrestin compared to G-protein, have been proposed to fulfill this role.
- However, oliceridine is the only drug that has been tested for its ability to produce analgesia, respiratory depression, abuse potential, and physical dependence in preclinical studies as well as large-scale clinical trials that have been evaluated by FDA.
- The data from these studies help inform whether the lack of interaction with beta-arrestin predicts an improved safety profile for a mu opioid agonist.

General Animal Behavioral Studies with Oliceridine

General behavioral tests are conducted as safety studies for all new drugs under development:

- In an evaluation of general behavior in rats, a 24 hour intravenous infusion of oliceridine at a high dose produced behavioral impairment, reduced food consumption, reduced body weight, and decreased forelimb grip strength relative to vehicle.
- In the rotorod test (which measures ability of a rat to hold onto a slowly rotating rod), oliceridine and morphine both produced a similar impairment in motor ability.

Animal Drug Discrimination Studies

- Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects.
- Test drugs that produce a response similar to a training drug with known abuse potential are also likely to be abused by humans.

Animal Drug Discrimination Study with Oliceridine

- In rats trained to discriminate morphine from vehicle:
  - Morphine produced full generalization (98%) to the morphine cue.
  - Oliceridine produced full generalization (75-99%) to the morphine cue.
- These data suggest that oliceridine produces sensations that are similar to morphine.
- This was expected, since oliceridine is a mu opioid agonist like morphine.

Animal Self-Administration Studies

- Self-administration is a method that assesses whether a test drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug (positive reinforcement).
- Drugs that are self-administered by animals are likely to produce rewarding effects in humans.
- The ability of a test drug to produce self-administration is indicative that the drug has abuse potential.

Animal Self-Administration Study with Oliceridine

- Rats were trained to lever-press for morphine as the training drug.
- After self-administration of morphine was stable, animals were allowed intravenous access to the following substances, which produced varying degrees of self-administration (infusions/session):
  - oliceridine (0.0125 and 0.04 mg/kg/infusion, i.v.) = 13-19 infusions
  - morphine (0.10-0.56 mg/kg/infusion) = 12-27 infusions
  - placebo = < 5 infusions
- These data show that oliceridine produces rewarding properties that sustain positive reinforcement, similar to morphine. This suggests that oliceridine has abuse potential.

Animal Physical Dependence Study with Oliceridine

- An animal physical dependence study was conducted in which rats received a continuous 14-day intravenous infusion of:
  - oliceridine (0.05, 0.15, 0.5 mg/kg/hr)
  - morphine (4 mg/kg/hr)
  - vehicle
- Observations were taken daily during drug administration and during the 7-day drug discontinuation phase.

Animal Physical Dependence Study Results

- During the drug discontinuation phase, both oliceridine and morphine produced the following statistically significant changes:
  - decrease in food consumption
  - decrease in body weight
  - classic opioid withdrawal signs including decreased locomotion, twitching, hunched posture, decreased muscle tone, vocalizing, aggression, and soft feces.
- These data show that prolonged administration of oliceridine produces opioid withdrawal signs after drug discontinuation, similar to that produced by morphine.

Need for a Human Abuse Potential Study

- The data show that oliceridine is a mu opioid agonist that consistently produces classic mu opioid agonist behavioral effects in animals.
- Mu opioid agonists are known to be drugs of abuse.
- This meant that it was necessary to conduct a human abuse potential study with oliceridine in order to provide definitive evidence of whether oliceridine produces rewarding effects in humans.

Human Abuse Potential Studies

- HAP studies evaluate the ability of a test drug to produce positive subjective responses in subjects compared to a known drug of abuse (with a similar mechanism of action) and to placebo.
- Subjects in HAP studies are individuals with a history of recreational drug use but they are not drug dependent.
- When the test drug produces consistently large responses on positive subjective scales that are far outside the acceptable placebo range, it is likely that the test drug has abuse potential.

Human Abuse Potential Study with Oliceridine

- The HAP study evaluated the abuse potential of a 1-minute intravenous infusion of:
    - Oliceridine (1, 2 and 4 mg)
    - Morphine (10 and 20 mg)
    - Placebo
- This study used a randomized, double-blind, placebo-controlled, crossover design in healthy non-dependent opioid abusers.
- Intravenous administration produces drug responses that occur immediately after administration, but monitoring for drug responses and adverse events continued for 24 hours.

Human Abuse Potential Study: Results

Primary Measure:

VAS Drug Liking (bipolar scale of 0 to 100, with 50 as neutral)

- The positive control drug, morphine (10 and 20 mg), produced statistically significantly higher mean Drug Liking scores (81 and 89, respectively) compared to placebo (51), which validates the study.
- Oliceridine at all three doses (1, 2, and 4 mg) produced mean Drug Liking scores (71, 83, and 88) that were statistically significantly higher than placebo (51) on Drug Liking.

Human Abuse Potential Study: Results

Secondary Measures:

VAS Overall Drug Liking, High, Good Drug Effects, Take Drug Again

- Morphine (10 and 20 mg) produced mean scores on each of these positive subjective measures that were statistically significantly greater than placebo.
- Oliceridine at all three doses (1, 2, and 4 mg) also mean scores on each of these positive subjective measures that were statistically significantly greater than placebo.

Human Abuse Potential Study: Results

Secondary Measures:

VAS Bad Drug Effects and Drowsiness

- Morphine (10 and 20 mg) and oliceridine (1, 2, and 4 mg) both produced mean scores on Bad Drug Effects that were within or close to the acceptable placebo range.
- Morphine and oliceridine both produced a dose-dependent increase in drowsiness that was outside the acceptable placebo range for each dose.

Human Abuse Potential Study: Results

Dose Comparisons:

- The 2 mg oliceridine dose produced similar responses to the 10 mg dose of morphine on all positive and negative subjective measures.
- The 4 mg oliceridine dose produced similar responses to the 20 mg dose of morphine on all positive and negative subjective measures.

Human Abuse Potential Study: Results

Drug Similarity:

- Oliceridine and morphine were both identified (respectively) as:
  - "Morphine or oxycodone" (72-84 points **vs.** 88-99 points)
  - "Codeine" (53-57 points **vs.** 11-34 points)
  - "Heroin" (37-40 points **vs**. 51-71 points)
- Thus, oliceridine was consistently identified as one of several opioids familiar to opioid abusers.

Human Abuse Potential Study: Abuse-Related Adverse Events

- Euphoria was reported at a high rate for both oliceridine (38-58% from 1, 2, and 4 mg) and morphine (50-69% from 10 and 20 mg).
- Somnolence was also reported at a high rate for both oliceridine (8-20% from 1, 2, and 4 mg) and morphine (15-33% from 10 and 20 mg).
- Paresthesia was also frequently reported for both oliceridine (3-8% from 1, 2, and 4 mg) and morphine (8-19% from 10 and 20 mg).
- Placebo did not produce any reports of these adverse events (0%).

Human Abuse Potential Study: Conclusions

- Oliceridine produced increases on positive subjective measures such as Drug Liking, Overall Drug Liking, High, Good Drug Effects and Take Drug Again that were far outside the acceptable placebo range.
- Oliceridine also was identified as an opioid and produced adverse events that included a high rate of euphoric effects (38-50%).
- These drug responses from oliceridine parallel those produced by the positive control drug, morphine.
- Thus, oliceridine produces classic opioid responses in healthy individuals with a history of opioid abuse that are similar to morphine.

FINAL CONCLUSIONS:
Abuse Potential of Oliceridine

- Animal and human studies consistently show that oliceridine is a mu opioid agonist with an abuse potential, overdose potential and ability to produce physical dependence that is similar to other mu opioid agonists such as morphine.
- Thus, CSS and the Applicant are in agreement that these data show that oliceridine has a high abuse potential.
- Therefore, it does not appear that the biased agonism of oliceridine with regard to preferential recruitment of G-protein over beta-arrestin translates into a human safety advantage for oliceridine compared to traditional mu opioid agonists.

FDA Presentations

- Introduction, Background, and Issues for Consideration
  - Elizabeth Kilgore, MD (Clinical Reviewer)
- Abuse Potential of Oliceridine
  - Katherine Bonson, PhD (Controlled Substance Staff Reviewer)
- Review of Efficacy
  - James Travis, PhD (Statistical Reviewer)
- Safety Assessment and Benefit/Risk Considerations
  - Elizabeth Kilgore, MD (Clinical Reviewer)


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Review of Efficacy

Anesthetic and Analgesic Drug Products Advisory Committee Meeting
October 11, 2018

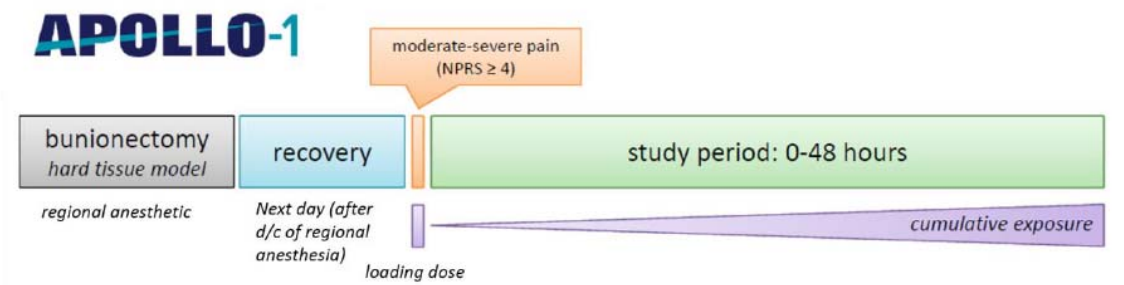
James Travis, PhD
Statistical Reviewer
Division of Biometrics II
Office of Biostatistics
Office of Translational Sciences (OTS)
CDER, FDA

Overview

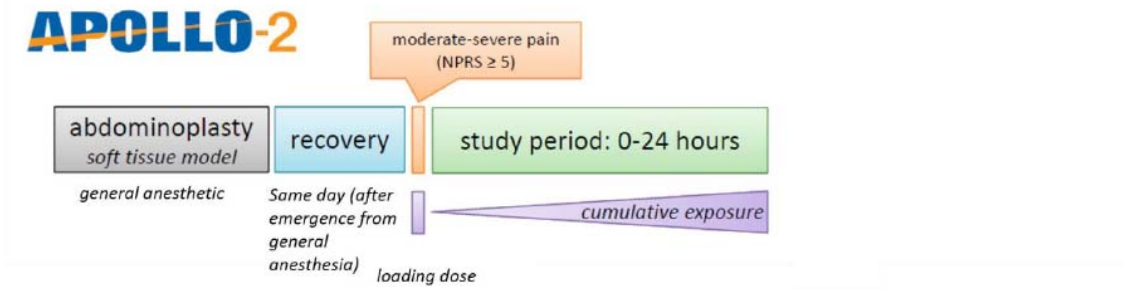
- Review the overall study design of the efficacy studies.
- Discuss the:
  - Applicant's efficacy analyses (responder endpoint)
  - FDA's efficacy analyses (SPID endpoint)
  - Applicant's analyses of the respiratory safety endpoint
  - Overall quantitative benefit-risk relationship for oliceridine

Study Design

3001



3002



d/c=discontinuation; NPRS/NRS=Numeric (Pain) Rating Scale

Clinical Program Objectives

- Evaluate the
  - Analgesic efficacy and safety of oliceridine compared to placebo
  - Safety and analgesic efficacy of oliceridine compared with morphine

Primary Efficacy Endpoint

- **Applicant**
  - The proportion of responders where responder defined as:
    - At least 30% improvement in Summed Pain Intensity Differences (SPID) score from baseline.
    - No use of protocol-specified rescue pain medication.
    - No early discontinuation of study medication.
    - Did not exceed the dosing limit of three PCA syringes or six clinician-administered supplemental doses within the first 12 hours.
- **FDA**
  - Examined the SPID component of the responder definition.

Key Secondary Safety Endpoint

- **Respiratory Safety Burden:** defined as the cumulative duration of respiratory safety events.
- A respiratory safety event was defined as any clinically relevant worsening of respiratory status determined by the investigator.

Dosing and Administration

Treatment Arms	Loading dose	PCA demand dose	Lockout Interval	Supplemental dose
Placebo	Volume-matched placebo solution	Volume-matched placebo solution		Volume-matched placebo solution
Oliceridine	1.5 mg	0.1 mg 0.35 mg 0.5 mg	6 minutes	0.75 mg q1 h PRN
Morphine	4 mg	1 mg		2 mg q1h PRN

- Supplemental clinician-administered oliceridine dosing PRN
- Rescue etodolac analgesic medication was allowed
- Extensive non-protocol specified analgesic rescue use

Efficacy Analyses

Primary Efficacy Analysis Methods

- The Applicant analyzed the responder rates using a logistic regression model, which included treatment group as a fixed factor, with baseline pain score and study site as covariates.
- The Hochberg multiplicity adjustment was used to control the type I error rate.
- Use of non-protocol specified rescue medication was not considered as non-response in the Applicant's original analysis.

Applicant's Responder Analysis – 3001

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	Morphine N=76
Responder, n (%)	12 (15.2%)	37 (48.7%)	46.9 (59.4%)	48 (60.8%)	48 (63.2%)
Odds Ratio of response vs placebo		5.4	8.4	8.8	9.8
95% CI		(2.5, 11.7)	(3.9, 18.3)	(4.0, 19.1)	(4.5, 21.6)
p-value vs placebo		<0.01	<0.01	<0.01	<0.01

Abbreviations: CI=confidence interval
Non-protocol specified rescue medication use was considered non-response

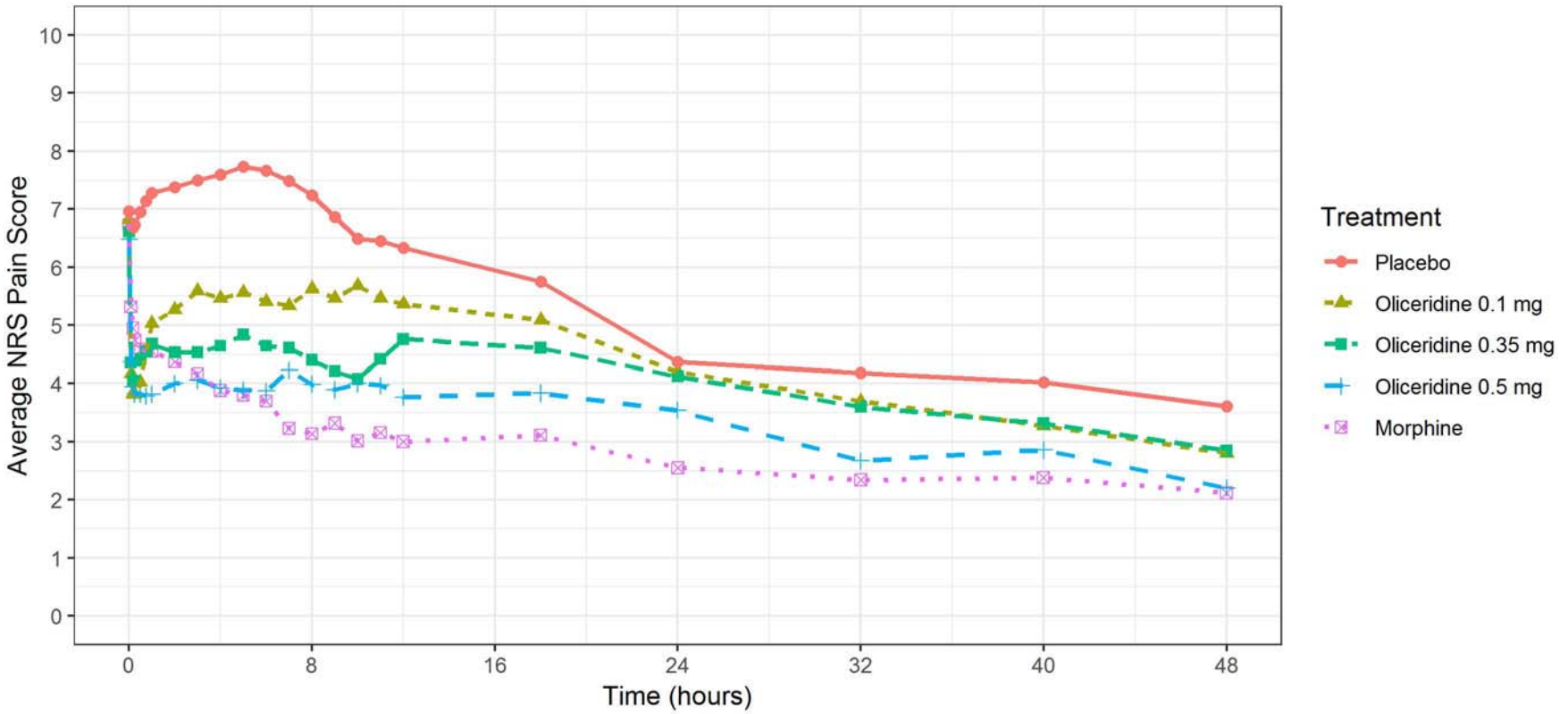
Responder Analysis vs Morphine – 3001

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	Morphine N=76
Responder, n (%)	12 (15.2%)	37 (48.7%)	46.9 (59.4%)	48 (60.8%)	48 (63.2%)
Odds Ratio of response vs morphine	0.10	0.55	0.86	0.89	
95% CI	(0.05, 0.22)	(0.28, 1.07)	(0.44, 1.66)	(0.46, 1.73)	
p-value vs morphine	<0.01	0.08	0.64	0.74	

FDA Analysis

- A key issue with the responder definition is that it truncates the improvement in SPID score, turning a continuous measure into a pass/fail, discarding important information. This is particularly important in the comparison with morphine and among the oliceridine doses.
- The responder definition will underestimate the effect in the populations that used more rescue medication.
- SPID scores were compared using an analysis of covariance (ANCOVA) model with treatment and site as factors and baseline pain score as a covariate.
- We used the following imputation scheme:
  - Pre-rescue pain scores were carried for 6 hours following use of rescue medication.
  - Observed scores were used where available after treatment discontinuation.
  - Intermittently missing pain scores will be imputed by linear interpolation.
  - Applicant's pre-specified method for missing data following treatment discontinuation.

Pain over Time – FDA Analysis – 3001



FDA Analysis – 3001

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	Morphine N=76
Estimated Mean SPID (SE)	85.0 (9.50)	131.6 (9.68)	138.1 (9.50)	163.7 (9.53)	192.6 (9.72)
Estimated mean diff. vs placebo (SE)		46.4 (13.51)	53.1 (13.41)	78.7 (13.44)	107.6 (13.54)
p-value vs placebo		<0.01	<0.01	<0.01	<0.01
Superiority vs placebo	-107.6 (13.54)	-61.1 (13.65)	-54.5 (13.52)	-28.9 (13.53)	
Estimated mean diff. vs morphine (SE)	<0.01	<0.01	<0.01	0.03	
p-value vs morphine	Yes	Yes	Yes	Yes	

Abbreviations: Diff=difference; SE=standard error

Applicant Analysis – 3002

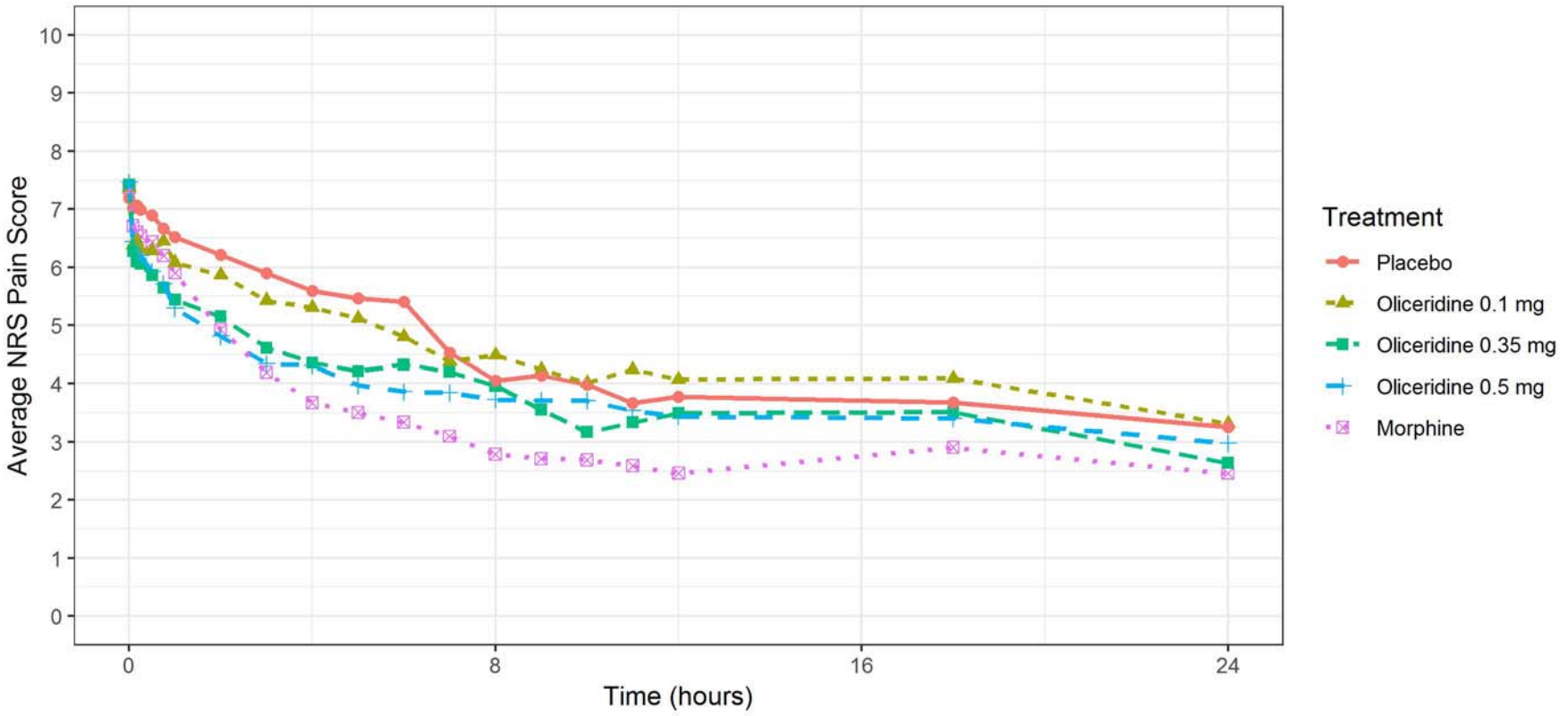
Statistic	Placebo N=81	Oliceridine 0.1 mg N=77	Oliceridine 0.35 mg N=80	Oliceridine 0.5 mg N=80	Morphine N=83
Responder, n (%)	33.1 (40.9%)	44.3 (57.5%)	55.8 (69.8%)	53.7 (67.1%)	61.7 (74.4%)
Odds Ratio of response vs placebo		2.2	4.2	3.7	5.3
95% CI		(1.1, 4.4)	(2.1, 8.6)	(1.8, 7.6)	(2.6, 11.0)
p-value vs placebo		0.03	<0.01	<0.01	<0.01

Non-protocol specified rescue medication use was considered non-response

Oliceridine vs Morphine – 3002

Statistic	Placebo N=81	Oliceridine 0.1 mg N=77	Oliceridine 0.35 mg N=80	Oliceridine 0.5 mg N=80	Morphine N=83
Responder, n (%)	33.1 (40.9%)	44.3 (57.5%)	55.8 (69.8%)	53.7 (67.1%)	61.7 (74.4%)
Odds Ratio of response vs morphine	0.19	0.42	0.79	0.71	
95% CI	(0.09, 0.39)	(0.20, 0.87)	(0.38, 1.67)	(0.34, 1.48)	
p-value vs morphine	<0.01	0.02	0.54	0.36	

Pain over Time – FDA Analysis – 3002



FDA Analysis – 3002

Statistic	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=76	Oliceridine 0.5 mg N=76	Morphine N=76
Estimated Mean SPID (SE)	74.8 (4.56)	76.8 (4.66)	89.72 (4.6)	94.0 (4.61)	103.0 (4.52)
Estimated mean diff. vs placebo (SE)		2.0 (6.20)	14.9 (6.18)	19.2 (6.21)	28.1 (6.11)
p-value vs placebo*		0.75	0.017	<0.01	<0.01
Superiority vs placebo		No	Yes	Yes	
Estimated mean diff. vs morphine (SE)	-28.1 (6.11)	-26.2 (6.16)	-13.24 (6.14)	-8.9 (6.17)	
p-value vs morphine	<0.01	<0.01	0.03	0.15	
Morphine superior	Yes	Yes	Yes	No	

*Using the Hochberg method gives a threshold of 0.025 for significance

Respiratory Safety

RSE Analysis Method

- First the proportion of patients within the treatment group having at least one RSE is modelled using the Firth logistic regression model.
- The cumulative duration was modelled using a gamma regression model for the patients who experienced at least one event.
- The provided model estimates are obtained by multiplying the model estimated proportion of patients with events by the model estimated cumulative duration.

Respiratory Safety Analysis Issues

- The objective was to evaluate whether there is a clinically meaningful benefit in respiratory safety with respect to morphine.
- The issues are:
  - FDA does not agree with this respiratory safety endpoint, primarily because respiratory safety events were not objectively defined and depended on clinical judgment.
  - Failed to show benefit over morphine for any oliceridine dose regimen.
  - Numerical trends in terms of respiratory safety must be considered in the context of the observed efficacy.
- We will also present an exploration of the quantitative benefit/risk relationship following the respiratory safety analyses.

Respiratory Safety Burden Analysis – 3001

Statistic (Hours)	Placebo N=79	Oliceridine 0.1 mg N=76	Oliceridine 0.35 mg N=79	Oliceridine 0.5 mg N=79	Morphine N=76
Mean (SD)	0 (0)	0.04 (0.33)	0.28 (1.11)	0.80 (3.33)	1.10 (3.03)
Maximum	0	2.88	6.43	24.4	16.6
Model-based estimate (95% CI)	-	0.02 (-0.03, 0.06)	0.15 (-0.02, 0.32)	0.25 (0.01, 0.48)	0.55 (0.08, 1.02)
Difference vs morphine (95% CI)	-	-0.53 (-0.99, -0.07)	-0.40 (-0.84, 0.04)	-0.30 (-0.75, 0.14)	
p-value vs morphine*	-	0.0241	0.0733	0.1786	

*Using the Hochberg adjustment gives a threshold of 0.0167 for significance

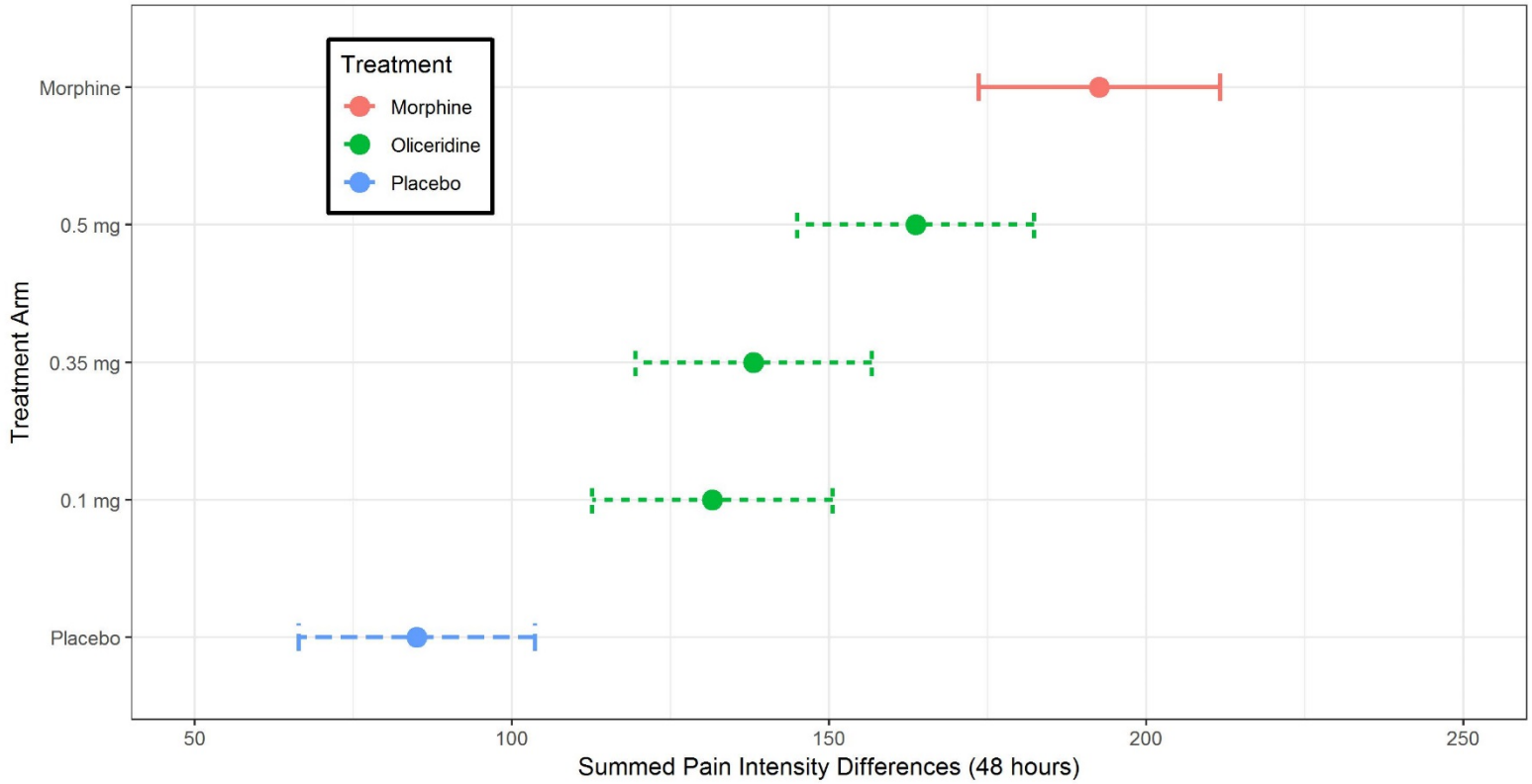
Respiratory Safety Burden Analysis – 3002

Statistic (Hours)	Placebo N=81	Oliceridine 0.1 mg N=77	Oliceridine 0.35 mg N=80	Oliceridine 0.5 mg N=80	Morphine N=83
Mean (SD)	0.60 (2.83)	0.43 (1.56)	1.48 (3.83)	1.59 (4.26)	1.72 (3.86)
Maximum	21.1	7.1	16.2	19.8	18.0
Model-based estimate (95% CI)	0.13 (-0.03, 0.29)	0.08 (-0.02, 0.19)	0.33 (0.05, 0.61)	0.43 (0.05, 0.82)	0.51 (0.09, 0.93)
Difference vs morphine (95% CI)	-0.38 (-0.76, -0.00)	-0.43 (-0.81, -0.04)	-0.18 (-0.54, 0.18)	-0.08 (-0.46, 0.31)	
p-value vs morphine*	0.05	0.03	0.33	0.70	

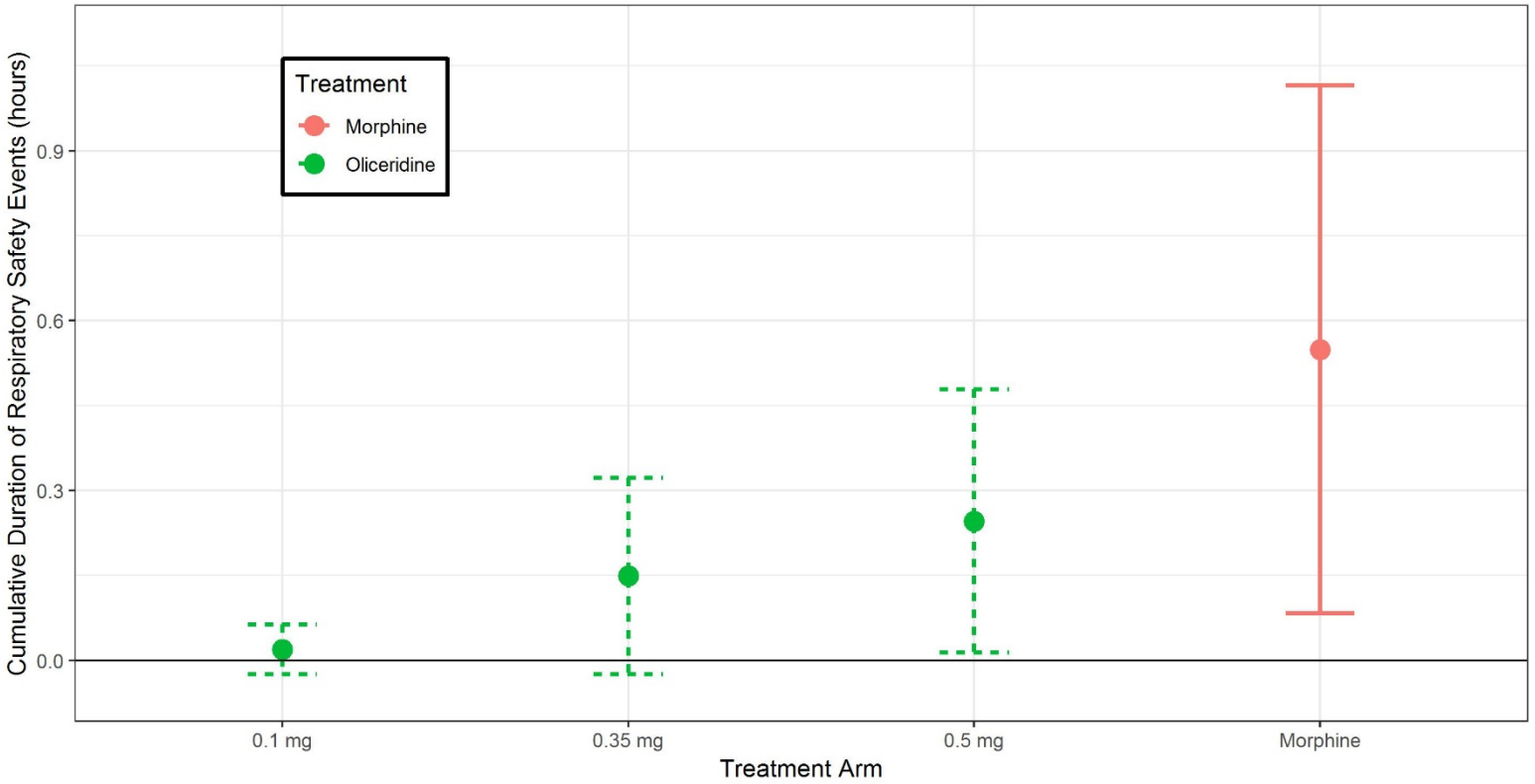
*Using the Hochberg adjustment gives a threshold of 0.0167 for significance

Quantitative Benefit/Risk Considerations

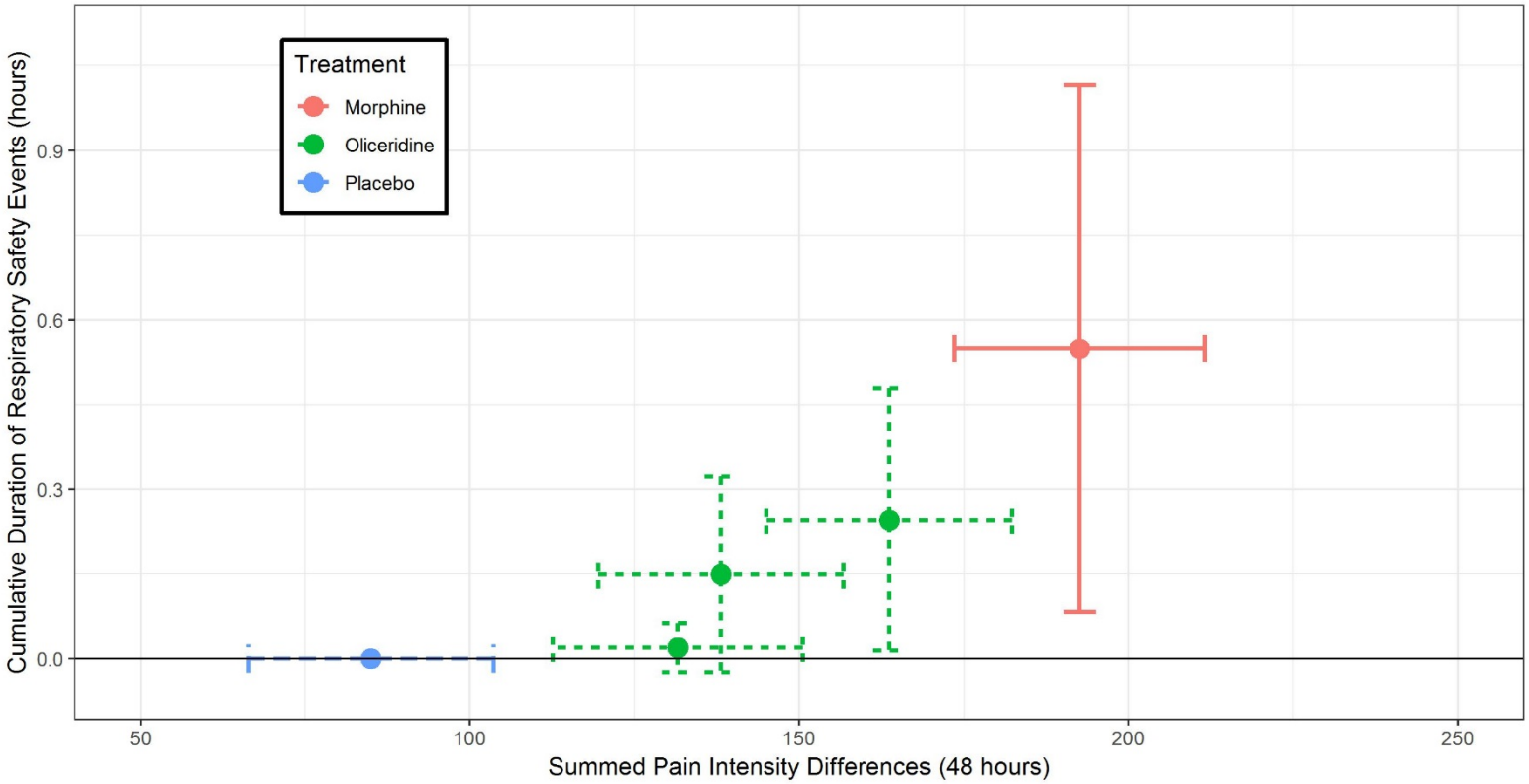
Efficacy Response – 3001



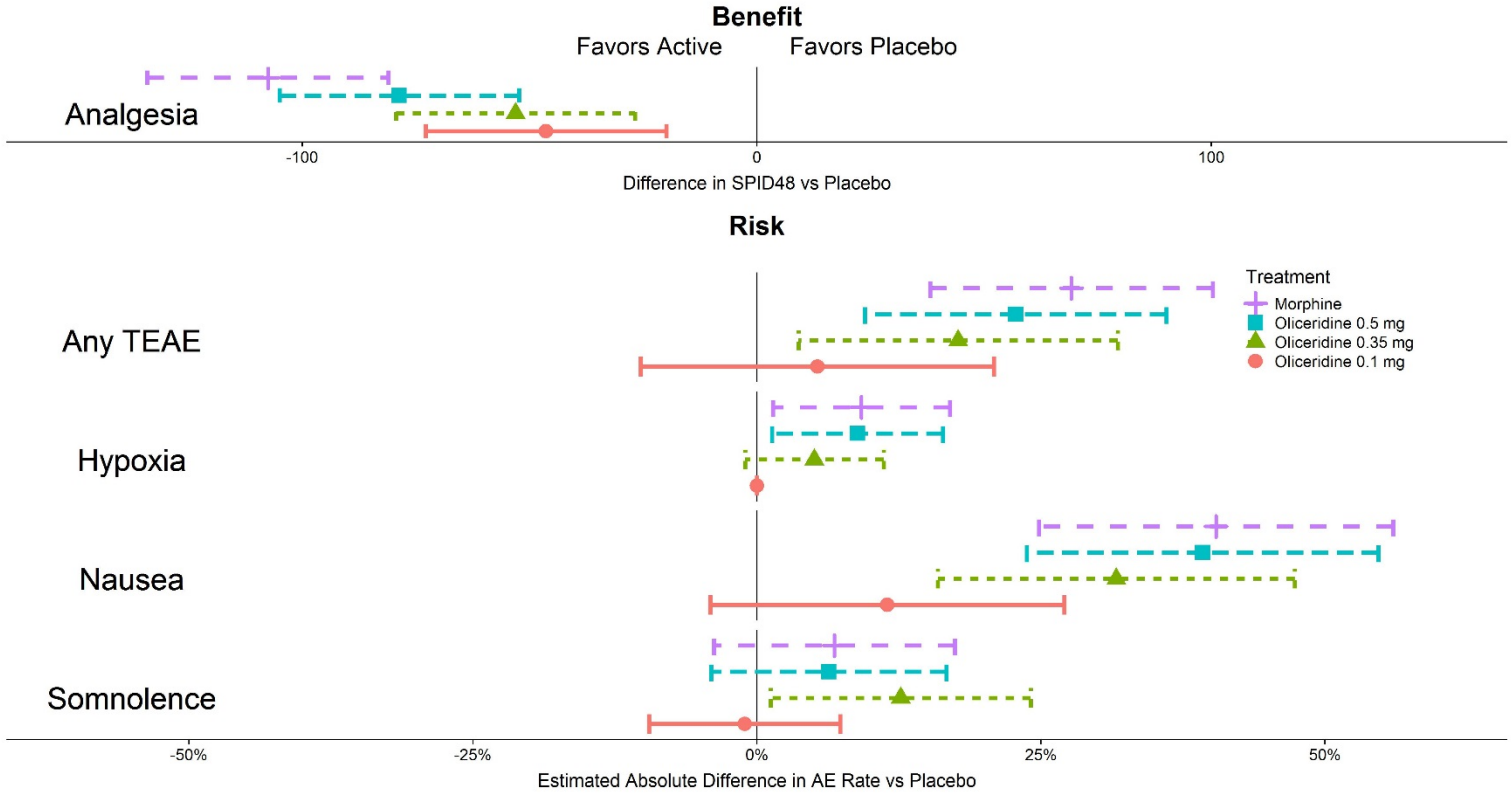
Respiratory Safety – 3001



Efficacy and Respiratory Safety Dose-Response – 3001



Benefit-Risk Plot – 3001



Conclusion

- There is replicated evidence of efficacy vs placebo in two studies for two oliceridine dose regimens (0.35 & 0.5 mg).
- There is a clear dose response for efficacy and safety for oliceridine.
- The efficacy of the selected doses of oliceridine was lower than the selected dose of morphine and has to be taken into account when assessing the comparative safety.
- There was no respiratory safety advantage for any of the doses of oliceridine compared to morphine.

FDA Presentations

- Introduction and Overview
  - Elizabeth Kilgore, MD (Clinical Reviewer)
- Abuse Potential of Oliceridine
  - Katherine Bonson, PhD (Controlled Substance Staff Reviewer)
- Review of Efficacy
  - James Travis, PhD (Statistical Reviewer)
- Safety Assessment and Benefit/Risk Considerations
  - Elizabeth Kilgore, MD (Clinical Reviewer)


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Safety Assessment and Benefit/Risk Considerations

Oliceridine

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

October 11, 2018

Elizabeth Kilgore, MD, MS

Overview of Clinical Safety Presentation

- Dosing in Phase 3 studies
- Exposure and safety database
- Key safety findings
- Submission specific safety findings
- Benefit/risk considerations

Dosing

Oliceridine Dosing in Phase 3 Controlled Studies and Phase 3 Open-Label Study

Phase 3 controlled studies (3001 and 3002)		
Loading dose	**PCA demand dose (PRN)**	**Supplemental dose**
1.5 mg	0.1 mg 0.35 mg 0.5 mg	0.75 mg q1 h PRN
Phase 3 uncontrolled study (3003)		
Bolus dosing	**PCA regimen**	**Rapid analgesia settings (e.g. ED or PACU)**
Initial dose: 1-2 mg Supplemental dose: 1 mg PRN Subsequent doses: 1-3 mg PRN q 1-3 h	Loading dose: 1.5 mg Demand dose: 0.5 mg PRN Supplemental dose: 1 mg PRN	Initial dose: 1-3 mg Supplemental dose: 1-3 mg PRN q 5 m Subsequent doses: 1-3 mg PRN q 1-3 h

Source: Agency-generated; PCA=patient-controlled analgesia, PRN=as needed, ED=emergency department, PACU=post-anesthesia care unit; m=minutes; h=hours.
All doses administered intravenously. There was a 6-minute lockout on the PCA doses.

Due to PRN dosing, there was a wide range of exposure to oliceridine.

How Dosing Affected Interpretation of Safety Data

- Patients could have received PRN oliceridine via patient controlled analgesia and/or clinician-administered doses
- As a result of this PRN dosing, even if a patient was randomized to one dose, the cumulative exposure to study drug varied
  - This was an important consideration when assessing exposure, safety findings, and dosing instructions in the proposed label

How Dosing Affected Agency's Safety Analysis

- Agency's primary safety analysis was the individual (not pooled) Phase 3 controlled studies by treatment regimen (placebo, morphine, and oliceridine 0.1 mg, 0.35 mg, and 0.5 mg) to consider:
  - the safety of the dose groups separately;
  - the safety results in the context of the efficacy results for a specific oliceridine dose;
  - key differences between Studies 3001 and 3002 with regard to patient populations, durations of treatment, and types of anesthesia used

Exposure

Extent of Exposure

- In the clinical program, a total of 1,853 unique individuals have been exposed to oliceridine
  - Of these, there were 1,535 patients with moderate-to-severe acute pain exposed in Phase 2 and Phase 3 studies

Dosing in Applicant's Proposed Label

2.2 Titration and Maintenance of Therapy

Individually titrate [BRANDNAME] to a dose that provides adequate analgesia and minimizes adverse reactions. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage.

Titration Phase

The initial dose of [BRANDNAME] should be 1 to 2 mg. Onset of analgesic effect is expected within 5 minutes of the initial dose. As multiple doses may be needed during titration, subsequent doses of 1 to 2 mg may be given as soon as 10 minutes after the previous dose based on individual patient need and previous response to [BRANDNAME].

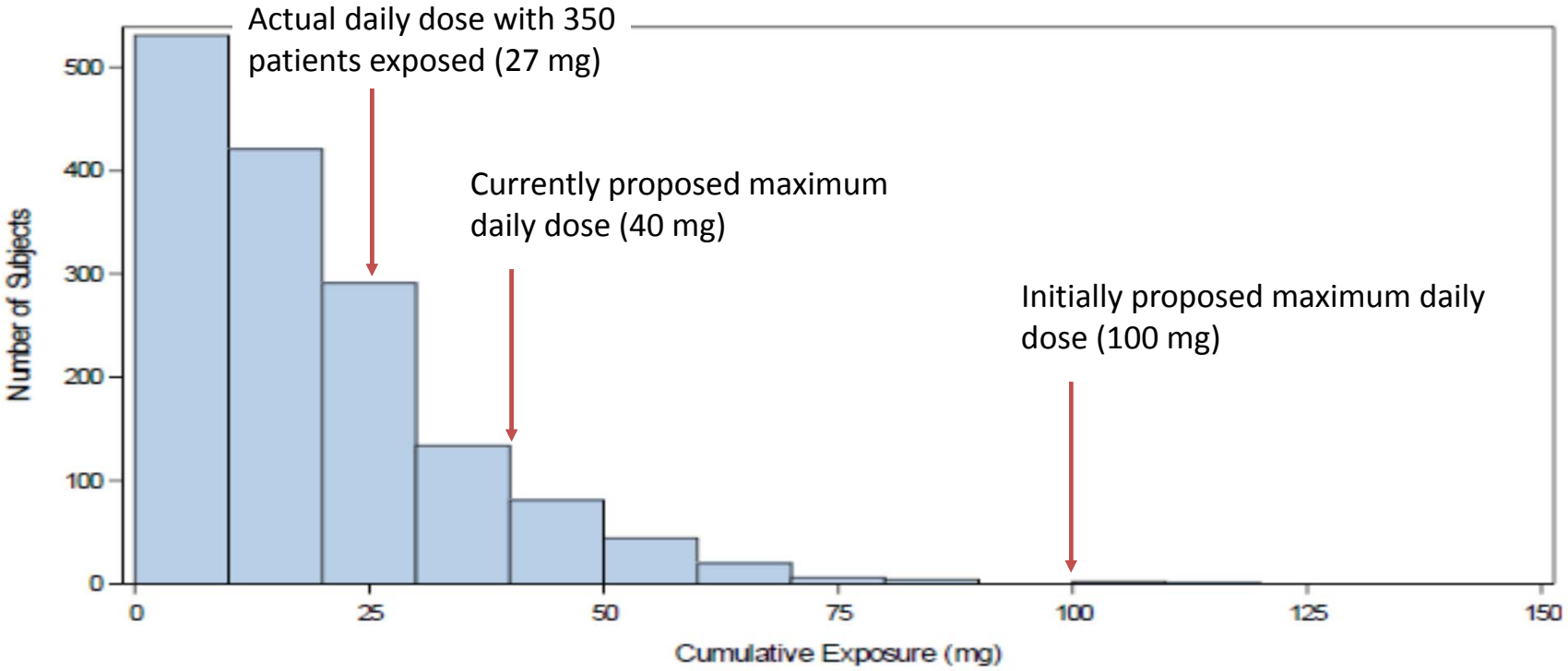
Maintenance Phase

Maintenance of analgesia is generally achieved with [BRANDNAME] administered as bolus doses of 1 to 2 mg every 1 to 3 hours as needed. Doses of 3 mg may be used in patients with more severe pain.

For patient-controlled analgesia (PCA) demand doses of 0.1 to 0.35 mg, with a 6-minute lockout, may be given as needed based upon patient response to initial bolus doses. Patients receiving multimodal therapy may be adequately treated with a lower demand dose. Supplemental bolus doses of 1 mg (as often as hourly, as needed) can also be used in conjunction with demand doses *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

Individual single doses greater than 3 mg and total daily dosages greater than 40 mg have not been adequately studied. If dosing above these levels is anticipated, patients should be monitored closely for signs of opioid-related adverse reactions.

Exposure in Pooled Phase 2 and 3 Studies Over First 24 Hours



- Applicant was advised they needed at least 350 patients exposed at highest planned dose
- Applicant initially proposed 100 mg daily, but few patients exposed
- Now Applicant proposes 40 mg daily, but exposure still lower than what FDA advised

Agency's Conclusions Regarding Safety Database

- Exposure database is smaller than the Agency's advice
- In the pooled Phase 2 and Phase 3 studies:
  - the highest dose that at least 350 patients were exposed to during the first 24 hours was 27 mg of oliceridine
  - the highest dose with the longest actual duration that had at least 350 patients exposed was 37.2 mg administered over an actual duration of at least 35.5 hours
- This exposure database does not appear adequate to support the proposed labeling that includes a maximum daily dose of 40 mg without a limit on the duration of use

Key Safety Findings

Overview of Key Safety Findings

- Deaths: There were no deaths in clinical development
- The following key safety events will be discussed:
  - Serious adverse events
  - Discontinuations due to adverse events
  - Common adverse events
  - Submission specific safety considerations

Serious Adverse Events (SAEs)

SAEs by Controlled Phase 3 Study

Study 3001					
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=79 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Number of patients with at least one SAE	0	0	0	0	0
Study 3002					
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Number of patients with at least one SAE	0	0	1 (1.3)	3* (3.8)	1 (1.2)

*There was one additional SAE in study 3002 (deep vein thrombosis) that occurred more than 7 days after the last dose of study medication identified in the Integrated Summary of Safety (ISS) but not included in the Clinical Study Report (CSR) due to a difference in the way the Applicant defined a treatment-emergent adverse event (TEAE) in the CSR and ISS, making a total of 4 cases in the 0.5 mg treatment arm using the ISS definition of treatment emergence.
Source: Agency-generated; From Applicant's data tables.

SAEs by Controlled Phase 3 Study

Study 3001					
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=79 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Number of patients with at least one SAE	0	0	0	0	0
Study 3002					
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Number of patients with at least one SAE	0	0	1 (1.3)	3* (3.8)	1 (1.2)

*There was one additional SAE in study 3002 (deep vein thrombosis) that occurred more than 7 days after the last dose of study medication identified in the Integrated Summary of Safety (ISS) but not included in the Clinical Study Report (CSR) due to a difference in the way the Applicant defined a treatment-emergent adverse event (TEAE) in the CSR and ISS, making a total of 4 cases in the 0.5 mg treatment arm using the ISS definition of treatment emergence.
Source: Agency-generated; From Applicant's data tables.

SAEs by Controlled Phase 3 Study

Study 3001					
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=79 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Number of patients with at least one SAE	0	0	0	0	0
Study 3002					
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Number of patients with at least one SAE	0	0	1 (1.3)	3* (3.8)	1 (1.2)

*There was one additional SAE in study 3002 (deep vein thrombosis) that occurred more than 7 days after the last dose of study medication identified in the Integrated Summary of Safety (ISS) but not included in the Clinical Study Report (CSR) due to a difference in the way the Applicant defined a treatment-emergent adverse event (TEAE) in the CSR and ISS, making a total of 4 cases in the 0.5 mg treatment arm using the ISS definition of treatment emergence.
Source: Agency-generated; From Applicant's data tables.

SAEs by Controlled Phase 3 Study

Study 3001					
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=79 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Number of patients with at least one SAE	0	0	0	0	0
Study 3002					
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Number of patients with at least one SAE	0	0	1 (1.3)	3* (3.8)	1 (1.2)

*There was one additional SAE in study 3002 (deep vein thrombosis) that occurred more than 7 days after the last dose of study medication identified in the Integrated Summary of Safety (ISS) but not included in the Clinical Study Report (CSR) due to a difference in the way the Applicant defined a treatment-emergent adverse event (TEAE) in the CSR and ISS, making a total of 4 cases in the 0.5 mg treatment arm using the ISS definition of treatment emergence.
Source: Agency-generated; From Applicant's data tables.

SAE Preferred Terms in Controlled Phase 3 Studies

- SAE preferred terms were post-operative or opioid-related
  - Oliceridine-treated (5 patients):
    - One case each of post-procedural hemorrhage, syncope, lethargy, abdominal wall hematoma, and deep vein thrombosis (DVT)
  - Morphine-treated (1 patient):
    - One patient experienced SAEs of pulmonary embolism and respiratory failure

SAE Preferred Terms in Open-Label Study 3003

- 26 patients (3.4%) experienced a total of 32 SAEs
- Types of SAEs fell into 3 broad clinical categories:
  - Post-operative (14 events)
  - Other (14 events)
  - Opioid-related (4 events)

Adverse Events (AEs) Leading to Discontinuation

AEs Leading to Discontinuation Controlled Phase 3

	Study 3001				
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=76 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Number of patients with at least one TEAE leading to early study medication discontinuation	0	0	1 (1.3)	5 (6.3)	6 (7.9)
	Study 3002				
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Number of patients with at least one TEAE leading to early study medication discontinuation	0	0	4 (5.1)	4 (5.0)	2 (2.4)

Source: Agency-generated based on Applicant's data tables; TEAE=treatment-emergent adverse event.

AEs Leading to Discontinuation Controlled Phase 3

	Study 3001				
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=76 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Number of patients with at least one TEAE leading to early study medication discontinuation	0	0	1 (1.3)	5 (6.3)	6 (7.9)
	Study 3002				
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Number of patients with at least one TEAE leading to early study medication discontinuation	0	0	4 (5.1)	4 (5.0)	2 (2.4)

Source: Agency-generated based on Applicant's data tables; TEAE=treatment-emergent adverse event.

AEs Leading to Discontinuation Controlled Phase 3

	Study 3001				
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=76 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Number of patients with at least one TEAE leading to early study medication discontinuation	0	0	1 (1.3)	5 (6.3)	6 (7.9)
	Study 3002				
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Number of patients with at least one TEAE leading to early study medication discontinuation	0	0	4 (5.1)	4 (5.0)	2 (2.4)

Source: Agency-generated based on Applicant's data tables; TEAE=treatment-emergent adverse event.

Preferred Term AEs Leading to Discontinuation Controlled Phase 3

	Study 3001		
Preferred Term	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
Oxygen saturation decreased	1 (1.3)	2 (2.5)	5 (6.6)
Hypoxia	0	2 (2.5)	0
Nausea	0	1 (1.3)	0
Dizziness	0	1 (1.3)	0
Sedation	0	1 (1.3)	0
Vomiting	0	0	1 (1.3)
	Study 3002		
Preferred Term	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Hypoxia	3 (3.8)	1 (1.3)	0
Nausea	0	1 (1.3)	0
Post procedural hemorrhage	0	1 (1.3)	0
Syncope	0	1 (1.3)	0
Hypotension	1 (1.3)	0	0
Non-cardiac chest pain	0	0	1 (1.2)
Presyncope	0	0	1 (1.2)

Source: Agency-generated based on Applicant's data tables. There were no discontinuations due to AEs in the placebo or oliceridine 0.1 mg treatment arms.

Preferred Term AEs Leading to Discontinuation Controlled Phase 3

	Study 3001		
Preferred Term	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
Oxygen saturation decreased	1 (1.3)	2 (2.5)	5 (6.6)
Hypoxia	0	2 (2.5)	0
Nausea	0	1 (1.3)	0
Dizziness	0	1 (1.3)	0
Sedation	0	1 (1.3)	0
Vomiting	0	0	1 (1.3)
	Study 3002		
Preferred Term	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Hypoxia	3 (3.8)	1 (1.3)	0
Nausea	0	1 (1.3)	0
Post procedural hemorrhage	0	1 (1.3)	0
Syncope	0	1 (1.3)	0
Hypotension	1 (1.3)	0	0
Non-cardiac chest pain	0	0	1 (1.2)
Presyncope	0	0	1 (1.2)

Source: Agency-generated based on Applicant's data tables. There were no discontinuations due to AEs in the placebo or oliceridine 0.1 mg treatment arms.

AEs Leading to Discontinuation Preferred Terms Open-Label Study 3003

- 17 patients (2.2%) patients experienced 29 AEs leading to discontinuation
- Preferred terms occurred across a wide range of clinical categories:
  - Allergic or pruritus (8 events)
  - Gastrointestinal (7 events)
  - Other (6 events)
  - Cardiac arrhythmia (3 events)
  - Hepatic disorders (2 events)
  - Hypotension (2 events)
  - Respiratory (1 event)

Common AEs

Common Adverse Events by Controlled Phase 3 Study

Study 3001					
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=76 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Patients with at least one TEAE	54 (68.4)	56 (73.7)	68 (86.1)	72 (91.1)	73 (96.1)
Study 3002					
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Patients with at least one TEAE	65 (78.3)	69 (89.6)	74 (93.7)	76 (95.0)	80 (97.6)

Source: Agency-generated based on review of Applicant's data tables.

Common Adverse Events by Controlled Phase 3 Study

Study 3001					
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=76 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
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Study 3002					
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
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Source: Agency-generated based on review of Applicant's data tables.

Common Adverse Events by Controlled Phase 3 Study

Study 3001					
	Placebo	**Oliceridine**			**Morphine**
	N=79 n (%)	0.1 mg N=76 n (%)	0.35 mg N=79 n (%)	0.5 mg N=79 n (%)	N=76 n (%)
Patients with at least one TEAE	54 (68.4)	56 (73.7)	68 (86.1)	72 (91.1)	73 (96.1)
Study 3002					
	Placebo	**Oliceridine**			**Morphine**
	N=83 n (%)	0.1 mg N=77 n (%)	0.35 mg N=79 n (%)	0.5 mg N=80 n (%)	N=82 n (%)
Patients with at least one TEAE	65 (78.3)	69 (89.6)	74 (93.7)	76 (95.0)	80 (97.6)

Source: Agency-generated based on review of Applicant's data tables.

Two Most Common AEs Oliceridine and Morphine

Study 3001					
Preferred Term	Placebo N=79 n (%)	Oliceridine 0.1 mg N=76 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
Nausea	19 (24.1)	27 (35.5)	44 (55.7)	50 (63.3)	49 (64.5)
Vomiting	5 (6.3)	13 (17.1)	31 (39.2)	32 (40.5)	38 (50.0)
Study 3002					
Preferred Term	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Nausea	38 (45.8)	34 (44.2)	49 (62.0)	60 (75.0)	61 (74.4)
Vomiting	11 (13.3)	18 (23.4)	17 (21.5)	34 (42.5)	44 (53.7)

Source: Agency-generated from Applicant's data tables.

Two Most Common AEs Oliceridine and Morphine

Study 3001					
Preferred Term	Placebo N=79 n (%)	Oliceridine 0.1 mg N=76 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
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Study 3002					
Preferred Term	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Nausea	38 (45.8)	34 (44.2)	49 (62.0)	60 (75.0)	61 (74.4)
Vomiting	11 (13.3)	18 (23.4)	17 (21.5)	34 (42.5)	44 (53.7)

Source: Agency-generated from Applicant's data tables.

Two Most Common AEs Oliceridine and Morphine

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Vomiting	5 (6.3)	13 (17.1)	31 (39.2)	32 (40.5)	38 (50.0)
Study 3002					
Preferred Term	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Nausea	38 (45.8)	34 (44.2)	49 (62.0)	60 (75.0)	61 (74.4)
Vomiting	11 (13.3)	18 (23.4)	17 (21.5)	34 (42.5)	44 (53.7)

Source: Agency-generated from Applicant's data tables.

Agency's Conclusions Regarding Adverse Events (Controlled Phase 3 Studies)

- All adverse events were generally dose-dependent in oliceridine-treatment groups
- In Study 3002, more patients in the oliceridine arms than the morphine arm discontinued due to hypoxia
- Common AEs for the oliceridine 0.5 mg arm had a similar percentage of patients with TEAEs as that of morphine
- The types of common TEAEs were similar (primarily opioid-related) in oliceridine- and morphine-treatment groups

Specific Safety Considerations

- Hepatic Safety
- Respiratory Safety
- QT Prolongation

Hepatic Safety

Select Hepatic Laboratory Findings Controlled Phase 3 Studies

Study 3001					
Patients with at Least One Abnormal Hepatic Laboratory Finding	Placebo N=79 n (%)	Oliceridine 0.1 mg N=76 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
AST or ALT ≥3xULN	1 (1.3)	0	2 (2.5)	1 (1.3)	1 (1.3)
AST or ALT ≥5xULN	0	0	2 (2.5)	0	1 (1.3)
Study 3002					
Patients with at Least One Abnormal Hepatic Laboratory Finding	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
AST or ALT ≥3xULN	0	3 (3.9)	3 (3.8)	1 (1.3)	3 (3.7)
AST or ALT ≥5xULN	0	2 (2.6)	2 (2.5)	0	2 (2.4)
AST or ALT ≥10xULN	0	2 (2.6)	1 (1.3)	0	0
AST or ALT ≥20xULN	0	1 (1.3)	0	0	0

Source: Agency-generated from Applicant's data tables. ; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ULN=upper limit of normal.

Select Hepatic Laboratory Findings Controlled Phase 3 Studies

Study 3001					
Patients with at Least One Abnormal Hepatic Laboratory Finding	Placebo N=79 n (%)	Oliceridine 0.1 mg N=76 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
AST or ALT ≥3xULN	1 (1.3)	0	2 (2.5)	1 (1.3)	1 (1.3)
AST or ALT ≥5xULN	0	0	2 (2.5)	0	1 (1.3)
Study 3002					
Patients with at Least One Abnormal Hepatic Laboratory Finding	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
AST or ALT ≥3xULN	0	3 (3.9)	3 (3.8)	1 (1.3)	3 (3.7)
AST or ALT ≥5xULN	0	2 (2.6)	2 (2.5)	0	2 (2.4)
AST or ALT ≥10xULN	0	2 (2.6)	1 (1.3)	0	0
AST or ALT ≥20xULN	0	1 (1.3)	0	0	0

Source: Agency-generated from Applicant's data tables; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ULN=upper limit of normal.

Select Hepatic Laboratory Findings on Treatment (All Phase 2 and Phase 3)

Patients with at Least One Abnormal Hepatic Laboratory Finding	Placebo N=252 n (%)	Total Oliceridine N=1535 n (%)	Morphine N=305 n (%)
AST or ALT ≥3xULN	4 (1.6)	32 (2.1)	6 (2.0)
AST or ALT ≥5xULN	1 (0.4)	17 (1.1)	4 (1.3)
AST or ALT ≥10xULN	1 (0.4)	8 (0.5)	1 (0.3)
AST or ALT ≥20xULN	0	4 (0.3)	0
Bilirubin ≥2xULN	0	10 (0.7)	0

Source: Agency-generated; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ULN=upper limit of normal.

Of the four patients with transaminase ≥20xULN, two cases were in open-label study 3003; 1 patient in controlled study 3002; and 1 patient in Phase 2 study 2001.

Select Hepatic Cases of Interest

Clinical Significance	Narrative Summary
Transaminase ≥3xULN with total bilirubin ≥2xULN	**Patient 1**: 70-year-old male s/p hiatal hernia repair Peak ALT=1,043 U/L (>26xULN) Peak AST=1,281 U/L (>37xULN) Total bilirubin=3.7 mg/dL (>2xULN) Cumulative dose was 6 mg over 15 h with onset Day 2
Transaminase ≥3xULN with total bilirubin ≥2xULN	**Patient 2:** 54 year-old-male s/p aortic arch repair Peak ALT=389 U/L (>6 x ULN) Peak AST=184 U/L (>4xULN) Total bilirubin=3.3 mg/dL (>2xULN) Cumulative dose was 25.5 mg over 28 h with onset Day 2
Serious Adverse Event Hepatic/Renal Failure	**Patient 3**: 55-year-old male s/p total knee arthroplasty Peak ALT=8,989 U/L (>160xULN) Peak AST=>21,000 U/L (>512xULN) Total bilirubin=1.4 mg/dL (not clinically significantly elevated) Cumulative dose was 23 mg over 30 h with onset Day 3

Source: Agency-generated; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; U/L=units/liter; dL=deciliter; h=hour.

Agency's Conclusions Regarding Hepatic Safety

- Phase 3 Controlled Studies:
  - Generally balanced frequency of elevated transaminases between oliceridine and morphine treatment groups
- Across all Phase 2 and Phase 3 studies (pooled):
  - There was a higher percentage of patients in the oliceridine group who experienced ≥20xULN transaminases compared to no cases in the placebo or morphine groups
  - Three cases of interest all occurred in Study 3003, which was open-label, without a comparator group, limiting conclusions
  - All three cases of interest appeared confounded possibly due to anesthesia and peri-operative medications
- Study 3003 was designed to represent a "real world" population of patients that may receive general anesthesia and multiple concomitant medications

Respiratory Safety

Respiratory Safety Results Controlled Phase 3 Studies

	Study 3001				
	Placebo N=79 n (%)	Oliceridine 0.1 mg N=76 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
Oxygen saturation <90%	1 (1.3)	3 (3.9)	8 (10.1)	11 (13.9)	15 (19.7)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	2 (2.5)	3 (3.9)	9 (11.4)	12 (15.2)	10 (13.2)
Patients with any O_2 administration	0	1 (1.3)	7 (8.9)	10 (12.7)	13 (17.1)
	Study 3002				
	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Oxygen saturation <90%	7 (8.4)	6 (7.8)	15 (19.0)	16 (20.0)	20 (24.4)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	9 (10.8)	9 (11.7)	23 (29.1)	25 (31.3)	25 (30.5)
Patients with any O_2 administration	5 (6.0)	6 (7.8)	16 (20.3)	18 (22.5)	23 (28.0)

Source: Agency-generated based on Applicant's data tables; O2=oxygen; SOC=System Organ Class.

Respiratory Safety Results Controlled Phase 3 Studies

	Placebo	Oliceridine 0.1 mg	Oliceridine 0.35 mg	Oliceridine 0.5 mg	Morphine
Study 3001					
	N=79 n (%)	N=76 n (%)	N=79 n (%)	N=79 n (%)	N=76 n (%)
Oxygen saturation <90%	1 (1.3)	3 (3.9)	8 (10.1)	11 (13.9)	15 (19.7)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	2 (2.5)	3 (3.9)	9 (11.4)	12 (15.2)	10 (13.2)
Patients with any O_2 administration	0	1 (1.3)	7 (8.9)	10 (12.7)	13 (17.1)
Study 3002					
	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Oxygen saturation <90%	7 (8.4)	6 (7.8)	15 (19.0)	16 (20.0)	20 (24.4)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	9 (10.8)	9 (11.7)	23 (29.1)	25 (31.3)	25 (30.5)
Patients with any O_2 administration	5 (6.0)	6 (7.8)	16 (20.3)	18 (22.5)	23 (28.0)

Source: Agency-generated based on Applicant's data tables; O2=oxygen; SOC=System Organ Class.

Respiratory Safety Results Controlled Phase 3 Studies

	Study 3001				
	Placebo N=79 n (%)	Oliceridine 0.1 mg N=76 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=79 n (%)	Morphine N=76 n (%)
Oxygen saturation <90%	1 (1.3)	3 (3.9)	8 (10.1)	11 (13.9)	15 (19.7)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	2 (2.5)	3 (3.9)	9 (11.4)	12 (15.2)	10 (13.2)
Patients with any O_2 administration	0	1 (1.3)	7 (8.9)	10 (12.7)	13 (17.1)
	Study 3002				
	Placebo N=83 n (%)	Oliceridine 0.1 mg N=77 n (%)	Oliceridine 0.35 mg N=79 n (%)	Oliceridine 0.5 mg N=80 n (%)	Morphine N=82 n (%)
Oxygen saturation <90%	7 (8.4)	6 (7.8)	15 (19.0)	16 (20.0)	20 (24.4)
TEAEs in Respiratory, thoracic, and mediastinal disorders SOC	9 (10.8)	9 (11.7)	23 (29.1)	25 (31.3)	25 (30.5)
Patients with any O_2 administration	5 (6.0)	6 (7.8)	16 (20.3)	18 (22.5)	23 (28.0)

Source: Agency-generated based on Applicant's data tables; O2=oxygen; SOC=System Organ Class.

Agency's Conclusions Regarding Respiratory Safety

- In Studies 3001 and 3002, there were dose-response relationships between increasing oliceridine dose and select respiratory parameters
- While there were trends showing a decreased percentage of respiratory events (as defined by the Applicant) with oliceridine compared to morphine for some parameters, this was not consistent across all parameters
- There are not sufficient data to support a conclusion that oliceridine has a respiratory safety advantage relative to morphine under the conditions studied

QT Prolongation

Thorough QT Study

- **General considerations:**
  - The purpose of the thorough QT study is to assess the effect of the drug on the QTc interval at doses that cover the high drug exposure scenario in patients
  - The translation of positive findings from a thorough QT study to predict the QT risk in patients depends on understanding the exposure response relationship and mechanism

Oliceridine Thorough QT Study Positive Findings

- Randomized, double-blind, 4-way crossover, placebo and positive-controlled, single-dose study
- Assessed the effects of oliceridine on the QTc interval at single doses of 3 and 6 mg
- Dose-proportional increase in QTc was observed ~1 h after time of peak plasma concentration
  - Mean QTc for 3 mg: 7 ms
  - Mean QTc for 6 mg: 12 ms

Limitations of Oliceridine Thorough QT Study

The Agency's review team cannot predict QT risk in patients for oliceridine:

- The QT study did not evaluate the maximum proposed dosing regimen, but showed a delayed increase in QTc following a single dose
- The mechanism of the delayed increase in QTc is unknown
- Nonclinical data show that the QTc prolongation may not be mediated via direct inhibition of the hERG potassium channels
- The exposure for the maximum proposed dosing regimen is projected to be 2 to 3-fold higher for the two major metabolites compared to highest dose in the thorough QT study

Limitation of Available ECG Data

- During development, the FDA advised the Applicant to conduct safety ECG monitoring at baseline, following the first dose, and periodically thereafter and that the timing of ECGs will need to reflect the delayed response relative to time of peak concentrations that was observed in the thorough QT study
- Upon review of the NDA, the Agency determined that the frequency of ECG assessments in the Phase 3 studies was limited and, therefore, we do not have adequate data from ECG monitoring to inform potential QT risk

Agency's Conclusions Regarding QT Prolongation

- Thorough QT study showed that single doses of oliceridine prolong the QTcF in a dose-dependent manner with a delayed onset
  - The delayed onset of QTcF prolongation suggests that the QTcF prolongation may not be mediated via direct inhibition of the hERG potassium channel by oliceridine or its major metabolites
  - The mechanism for the delayed onset of the QTcF prolongation observed with oliceridine remains unclear
- The submitted data are not adequate to evaluate the QT effects of oliceridine for the maximum proposed dosing regimen

Benefit/Risk Considerations

Agency's Conclusions Regarding Benefit/Risk

- The Agency's conclusions are based primarily on analyses by randomized treatment group in the individual studies to have a clinically relevant understanding of the safety and efficacy data by oliceridine dose
- It is important to understand the relative efficacy of a specific dose when considering the safety of that dose

Agency's Conclusions Regarding Benefit/Risk (2)

- Comparisons to placebo
  - Oliceridine demonstrated statistically significantly greater reduction in pain
  - In general, adverse events were dose-related and consistent with an opioid-safety profile
- Comparisons to morphine
  - The oliceridine doses that had fewer adverse events than morphine also were less effective than morphine
  - There does not appear to be data to support a conclusion that oliceridine has a safety advantage compared to morphine under the conditions studied


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ADMINISTRATION

Backup Slides Shown

Rescue Medication Types

APOLLO-1 Rescue Medication Types

Treatment Arm	Number (%) of patients with any rescue usage
Etodolac (Protocol Specified)	236
Ibuprofen	14
Oxycodone	9
Hydrocodone/APAP 5/325 mg	9
Hydrocodone/APAP	6
Hydrocodone/APAP 7.5/325 mg	3
APAP	1
Ketorolac	1
Hydrocodone/APAP 5/300 mg	1

APOLLO-2 Rescue Medication Types

Treatment Arm	Number (%) of patients with any rescue usage
Etodolac (protocol specified)	105
Hydrocodone/APAP 5/325mg	7
APAP	5
Hydrocodone/APAP	3
Oxycodone	3
Hydrocodone/APAP 5/300 mg	1