Potential for Reduced Postoperative Ileus with Use of Oliceridine, An IV Opioid Analgesic, In Colorectal Surgery

eP407

Timothy L. Beard, MD, FACS[1], Cathy Michalsky, MS[2], Kanaka Sridharan, MS[2], Erik DeBoer, PhD[2], Suzanne Griffith, RN[3], Paul Rider, MD, FACS, FASCRS[4]

[1]Summit Medical Group, Bend Memorial Clinic, Bend, OR, USA. [2]Trevena Inc., Chesterbrook, PA, USA. [3]Research Partners, Inc., Jackson, MS, USA. [4]University of South Alabama Medical Center, Mobile, AL, USA.

TAMPA FLORIDA
ASCRS ANNUAL SCIENTIFIC MEETING

BACKGROUND

- Postoperative ileus (POI) is a serious debilitating complication following abdominal or colorectal surgery.[1]
- It is characterized by abdominal distention and bloating, nausea, vomiting, pain, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defecation.[2]
- Use of IV opioid analgesics can further exacerbate POI, prolong length of stay, and increase morbidity.[3,4]
- The incidence of POI following colectomy, cholecystectomy, or other abdominal surgeries is reported at 10 to 30%.[4]
- Alvimopan is a peripherally acting μ-opioid receptor antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following partial bowel resection surgery with primary anastomosis.[5]
  - In clinical studies for the management of POI, alvimopan was administered orally at doses of 12 mg preoperatively and continued following surgery for up to 7 days for a maximum of 15 doses.
  - Data from Phase 3 studies of alvimopan report a 12% incidence of POI with use of IV opioids (placebo group) and with use of alvimopan the incidence was 5 to 6%.[6]
- Oliceridine, a new class of IV opioids, that is a G protein-selective agonist at the μ-opioid receptor, was recently approved for use in adults for the management of acute pain severe enough to require an IV opioid analgesic and for whom alternative treatments are inadequate.[7]
- Preclinical findings showed that oliceridine is selective for G-protein signaling (achieving analgesia) with limited recruitment of β-arrestin (pathway associated with opioid-related adverse events [ORAEs]), resulting in robust analgesia with reduced adverse events(AEs).[8] The translation of these findings in humans has not been fully established.

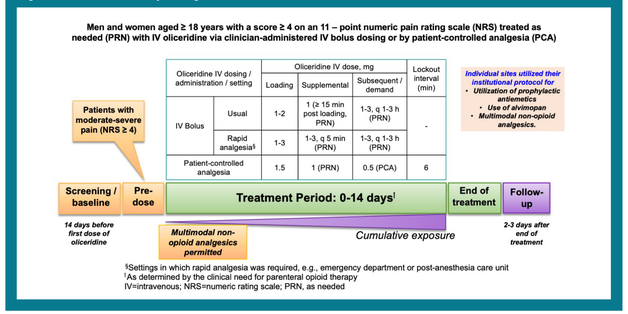
Hypothesis: Oliceridine may be associated with a lower incidence of POI.

OBJECTIVE

- In an exploratory analysis, we evaluated the incidence of observed or self-reported ORAEs of constipation or POI with oliceridine from the Phase 3 open-label safety study (ATHENA) (**Figure 1**) in a sub-population of patients who underwent colorectal surgery.

METHODS

Figure 1: ATHENA Study Design and Treatment Protocol



- Individual sites followed their institutional protocol for utilization of prophylactic antiemetics, alvimopan, and multimodal non-opioid analgesics.

Exploratory analysis

- We evaluated the incidence of observed or self-reported AEs of constipation or POI with oliceridine, coded based on verbatim reported terms, using Medical Dictionary for Regulatory Activities (MedDRA, V 19.0) in patients undergoing colorectal surgical procedures.
- For this analysis, patients who underwent colon resections (including colostomy, ileostomy, proctectomy, sigmoidectomy, rectum removal and duodenoplasty) were included in the analysis.
- We report the incidence stratified by use of alvimopan.

RESULTS

- A total of 768 patients were enrolled in the ATHENA trial.
- 108 patients underwent colon resections (including colostomy, ileostomy, proctectomy, sigmoidectomy, rectum removal, and duodenoplasty) (Table 1).
- 79/108 patients (73%) received alvimopan and demographic characteristics are shown on Table 2.

Table 1: Colorectal Surgical Procedures

	N=108
Open colon resection with anastomosis	53
Laproscopic/Robotic colon resections	42
Open colon resections with ostomy	11
Laparoscopic colostomy reversal	2

- Time to bowel function return was recorded in one site for 29 patients undergoing colorectal surgery treated with oliceridine (***5 of these patients did not receive alvimopan***) and 16 patients treated with standard of care, conventional opioids (matched cohort).

Table 2: Demographic Characteristics

Characteristic	Received Alvimopan N=79	Did Not Receive Alvimopan N=29
Age, mean (SD) years, n (%)	60.6 (11.3)	60.2 (12.7)
Sex, n (%)		
Female	**42 (53.1)**	**17 (58.6)**
Male	37 (46.8)	12 (41.4)
Race, n (%)		
White	65 (82.3)	17 (58.6)
Black or African American	13 (16.4)	10 (34.5)
Asian	1 (1.3)	1 (3.4)
American Indian or Alaska Native	0	1 (3.4)
BMI, mean (SD) kg/m²		
< 30	49 (62.0)	17 (58.6)
30 - 40	27 (34.2)	10 (34.5)
> 40	3 (3.8)	2 (6.9)
Baseline Pain Score, mean (SD)	5.9 (2.3)	6.7 (2.6)

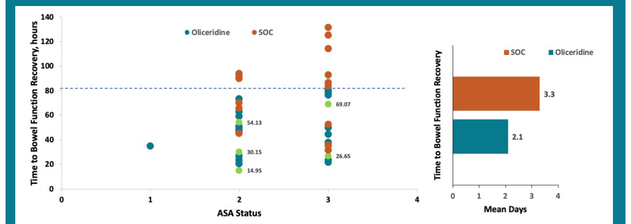
- The mean (SD) cumulative dose of oliceridine and the duration in the two groups is shown in Table 3. Patients receiving alvimopan had a longer duration of exposure than patients not receiving alvimopan (median hours: 56.5 vs 45.5).

Table 3: Exposure to Oliceridine

	Received Alvimopan N=79	Did Not Receive Alvimopan N=29
Oliceridine Total Cumulative Dose (mg)		
Mean (SD)	**50.1 (37.7)**	**47.3 (36.4)**
Median	41.5	37.9
Minimum, Maximum	2, 165	3, 138.6
Total Oliceridine Duration (hours)		
Mean (SD)	56.5 (28.9)	45.5 (33.1)
Median	56.3	43.1
Minimum, Maximum	0, 142.7	0, 138.3

- Figure 2 shows the scatter plot for time in hours to bowel function return by patient ASA status.

Figure 2: Time to Bowel Function Recovery by ASA Status

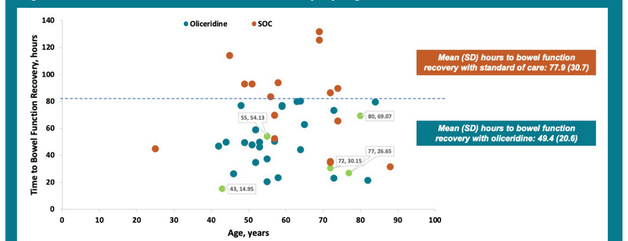


Five patients NOT receiving alvimopan in the oliceridine group (3 cases of colectomy, one case of ileostomy and one case of proctectomy)

ASA status, American Society of Anesthesiologists' Physical Status Classification; SOC, standard of care.

- Figure 3 shows the scatter plot for time in hours to bowel function return by patient age.

Figure 3: Time to Bowel Function Recovery by Age



Five patients NOT receiving alvimopan in the oliceridine group (3 cases of colectomy, one case of ileostomy and one case of proctectomy)

SOC, standard of care.

- Incidence of constipation and POI are shown in Table 4.
- Among the 34 patients who did not receive alvimopan, none experienced POI (Table 4).

Table 4: Incidence of Constipation and POI in Patients Receiving Oliceridine Stratified by use of Alvimopan

	Received Alvimopan N=79	Did Not Receive Alvimopan N=29
Constipation	11 (13.9%)	2 (6.9%)
Ileus	2 (2.5%)	0

LIMITATIONS

- The exploratory findings reported here are based on post-randomization events and the adverse events collected were spontaneously reported.

CONCLUSIONS

- These preliminary findings suggest a trend towards lower incidence of postoperative ileus with IV oliceridine.
- Data from an additional exploratory analysis at one site comparing standard of care at their institution, showed median time to bowel function recovery of 2.0 days with oliceridine and 3.5 days with use of conventional opioids.
- Future well designed trials are needed to confirm these preliminary findings.

REFERENCES

1. Sanfilippo F and Spoletini G (2015). *Curr Med Res Opin.* 31(4): 675-676.
2. Chamie K, Golla V, Lenis AT, et al (2021). *J Gastrointest Surg.* 25(1): 293-302.
3. Simpson JC, Bao X, Agarwala A (2019). *Clin Colon Rectal Surg.* 32(2): 121-128.
4. Gan TJ, Robinson SB, Oderda GM, et al (2015). *Curr Med Res Opin.* 31(4): 677-686.
5. ENTEREG® Prescribing Information, Merck & Co., Inc, 2022.
6. Beattie, DT. (2009). *Clin Med Ther.* 1: CMT.S2384.
7. OLINVYK® Prescribing Information. Trevena, Inc.; 2021.
8. DeWire SM, Yamashita DS, Rominger DH, et al. (2013). *J Pharmacol Exp Ther.* 344(3): 708-717.

DISCLOSURES AND ACKNOWLEDGEMENTS

- ATHENA Study: NCT02656875.
- Layout for the poster was provided by Innovation Communications Group.