

Entereg[®] (alvimopan) Capsules for the Management of Postoperative Ileus Safety

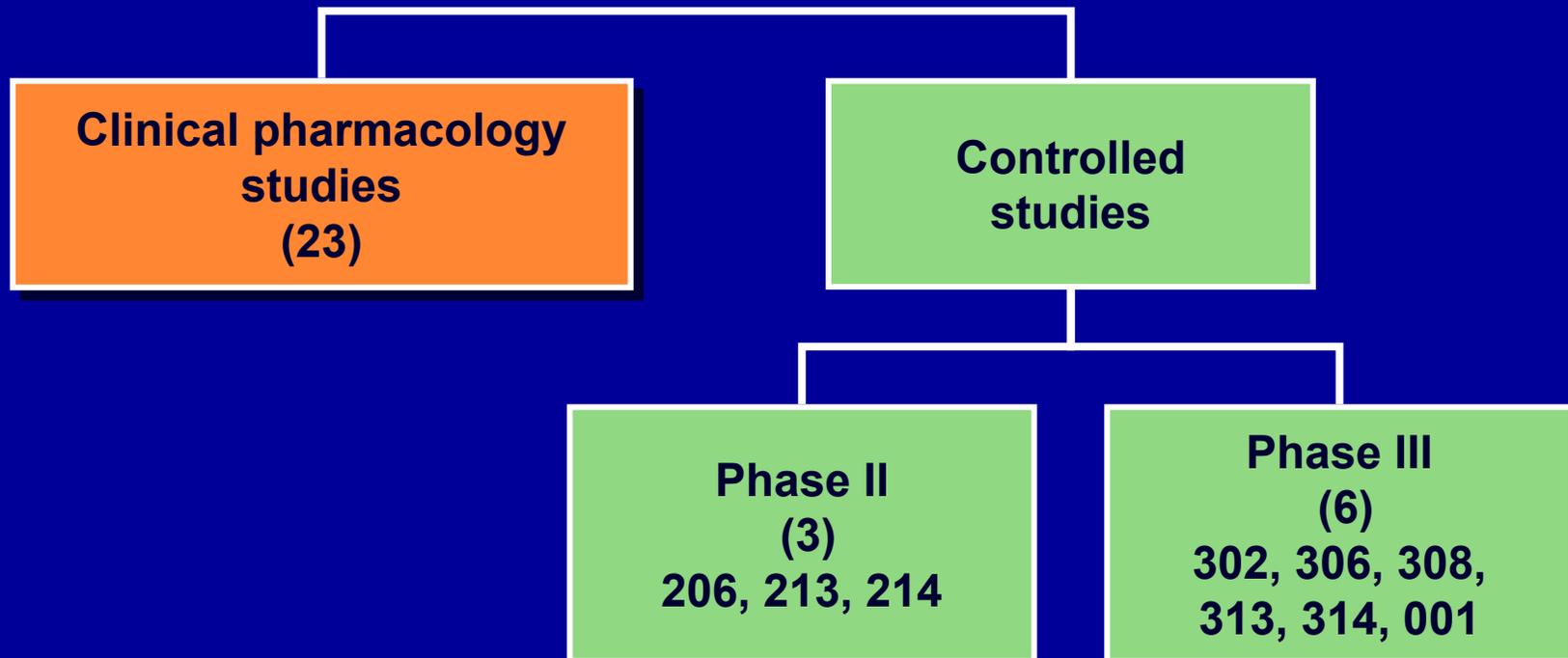
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POI Safety Presentation Outline

- ❖ Safety analysis population
- ❖ Treatment-emergent and serious AEs
- ❖ Evaluation of CV, fracture, and neoplasia AEs
- ❖ Follow-up in POI studies

Safety Presentation Analysis Populations



- ⌘ Patients who underwent BR or TAH
- ⌘ Patients who received placebo or alvimopan 1 - 3 mg,^a 6 mg, or 12 mg

^a Disposition only.

Patient Disposition

Worldwide POI Safety Population

| | Patients, % | | | |
|-----------------------------|---------------------|--------------------|-----------------|-------------------|
| | Placebo n = 1365 | Alvimopan | | |
| | | 1 - 3 mg n = 62 | 6 mg n = 898 | 12 mg n = 1650 |
| Completed treatment | 76.5 | 79.0 | 80.8 | 82.7 |
| Discontinued from treatment | 23.5 | 21.0 | 19.2 | 17.3 |
| Adverse event | 11.1 | 11.3 | 7.7 | 7.6 |
| Other | 12.4 | 9.7 | 11.5 | 9.6 |

Treatment-emergent AEs $\geq 10\%$ in Any Group Worldwide POI Safety Population

| Preferred term ^a | Patients, % | | |
|-----------------------------|---------------------|-----------------|-------------------|
| | Placebo n = 1365 | Alvimopan | |
| | | 6 mg n = 898 | 12 mg n = 1650 |
| Nausea | 51.2 | 40.9 | 52.0 |
| Vomiting | 21.9 | 16.9 | 18.5 |
| Abdominal distension | 13.0 | 8.8 | 10.7 |
| Pyrexia | 13.8 | 9.4 | 10.0 |
| Hypertension | 10.5 | 11.1 | 10.4 |

^a Patients with > 1 AE in same category counted only once.

Serious AEs

Worldwide POI Safety Population

| Preferred term ^a | Patients, % | | |
|------------------------------|---------------------|-----------------|-------------------|
| | Placebo n = 1365 | Alvimopan | |
| | | 6 mg n = 898 | 12 mg n = 1650 |
| Postoperative ileus | 4.4 | 1.2 | 0.8 |
| Small intestinal obstruction | 1.9 | 0.8 | 1.2 |
| Postoperative infection | 1.4 | 1.1 | 1.1 |
| Postoperative abscess | 1.1 | 1.3 | 0.7 |
| SAEs resulting in death | 0.7 | 0.6 | 0.5 |

^a Patients with > 1 AE in same category counted only once.

Cardiovascular Safety of Alvimopan— POI Program

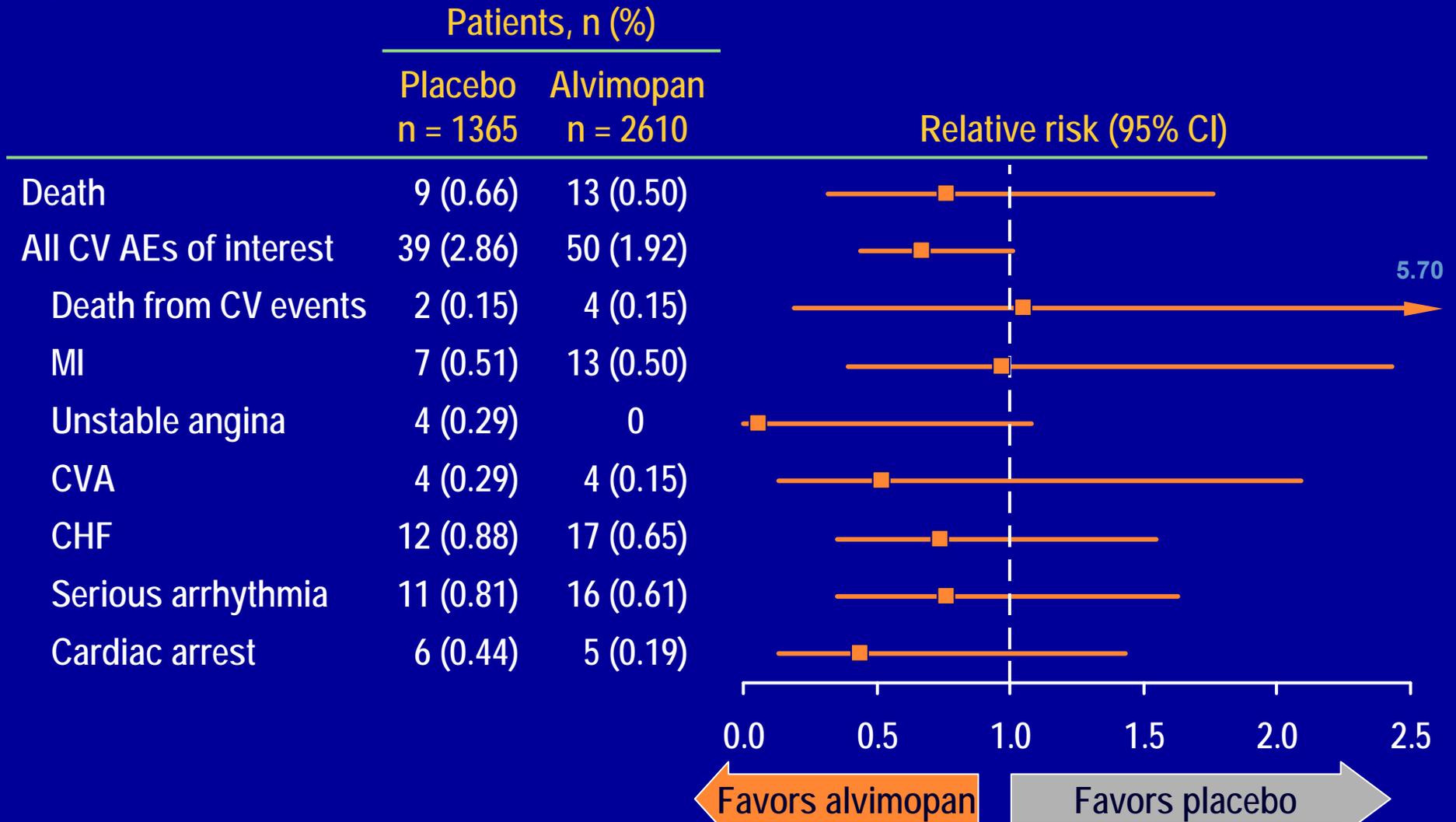
- ❖ **Based on numerical imbalance of MIs in the alvimopan treatment group (0.5 mg BID) in a long-term OBD Study, GSK014**
 - **FDA requested collection of additional source documentation (eg, ECG tracings, cardiac biomarkers) for POI patients with CV events of interest (as defined by FDA)**
 - **Objective: evaluate balance of CV AEs across treatment groups by case adjudication**

CV Adverse Events of Interest Categories

- ❖ Death (all cause)
- ❖ Death from CV events
- ❖ Myocardial infarction^a (MI)
- ❖ Unstable angina
- ❖ Cerebrovascular accident^a (CVA)
- ❖ Congestive heart failure^a (CHF)
- ❖ Serious arrhythmia^a
- ❖ Cardiac arrest^a

^a Includes fatal and nonfatal events.

Incidence of CV Events of Interest Worldwide POI Safety Population



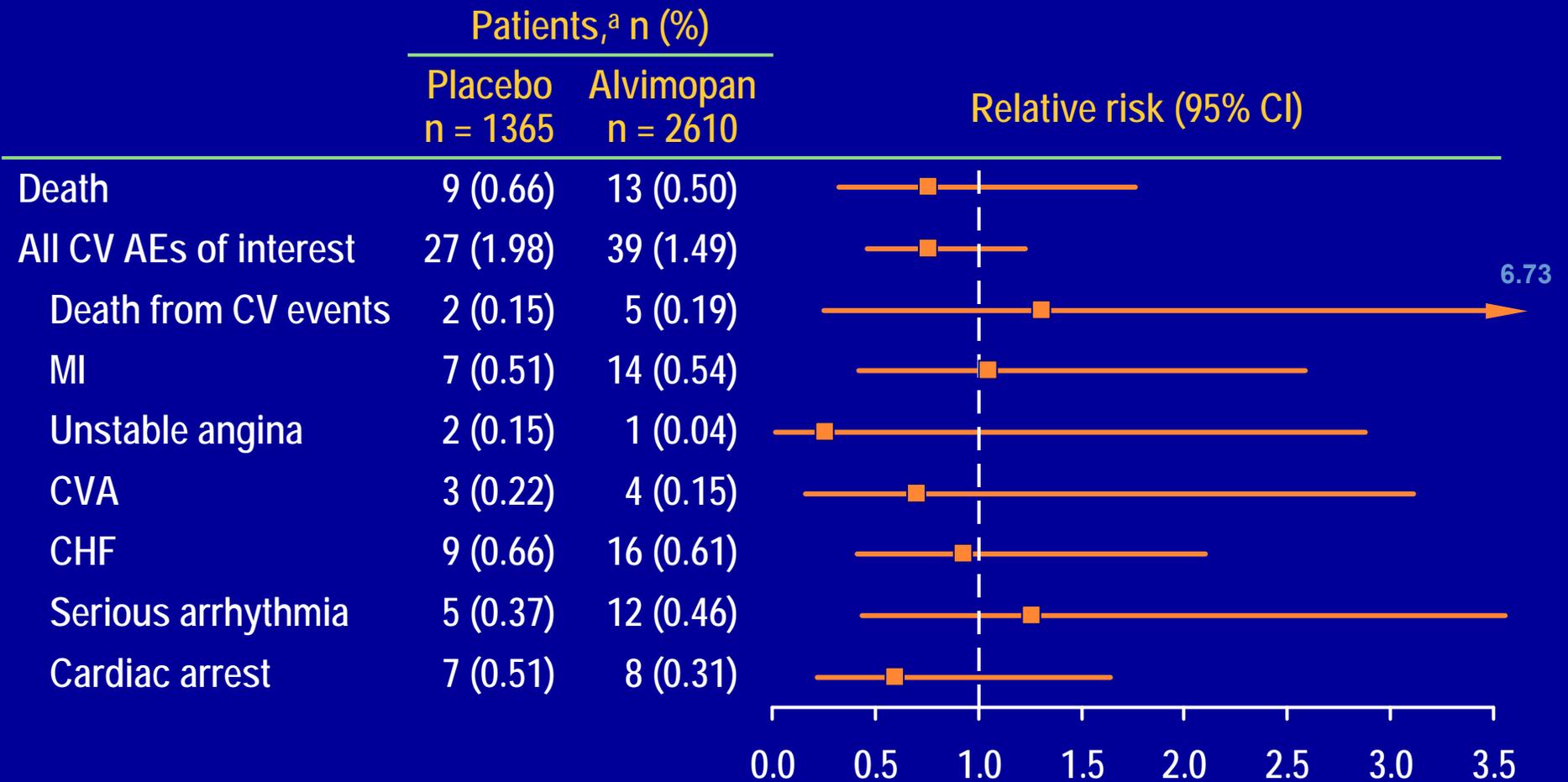
Deaths of unknown cause included in CV death category.

Duke Clinical Research Institute Clinical Events Committee (CEC)

- ❖ Independent, blinded adjudication of all POI CV AE cases**
 - Patient-level source documentation**
- ❖ CEC charter and specific event definitions**
 - AHA/ACC guidelines**
 - Clinical judgment**
- ❖ CEC team consisted of practicing physicians specializing in cardiology or neurology**

Incidence of CV Events of Interest

DCRI Adjudication Results



Deaths of unknown cause included in CV death category.

^a Patients may appear in ≥ 1 category.

Estimate of MI Following Bowel Resection Using NSQIP Database

- ⌘ 19,895 colectomy patients identified by CPT codes^a
- ⌘ 1991 - 1999
- ⌘ 30-day morbidity/mortality

| | POI safety population, BR | | DCRI adjudication results, BR | | VA NSQIP database |
|---------------------|---------------------------|-----------|-------------------------------|-----------|-------------------|
| | Placebo | Alvimopan | Placebo | Alvimopan | |
| Patients, n | 986 | 1681 | 986 | 1681 | 19,985 |
| Patients with MI, % | 0.71 | 0.71 | 0.71 | 0.71 | 0.96 |

NSQIP = National Surgical Quality Improvement Program.

^a Khuri SF, et al. *Ann Surg.* 2005;242:326-343.

Fracture Treatment-emergent AEs

Worldwide POI Safety Population

| Preferred term | Patients, n (%) | | |
|----------------|---------------------|------------------------------|--------------------------------|
| | Placebo n = 1365 | Alvimopan 6 mg n = 898 | Alvimopan 12 mg n = 1650 |
| Rib fracture | 0 | 0 | 1 (< 0.1) |

This 84 year-old female patient (14CL314.39.00178) experienced a fracture of the left 4th, 5th, and 6th ribs associated with syncope and a fall on postoperative day 9 following bowel resection surgery.

Neoplasm Treatment-emergent AEs

Worldwide POI Safety Population

SOC neoplasms benign, malignant, and unspecified (including cysts and polyps)

| System organ class Preferred term ^a | Placebo n = 1365 | Alvimopan | | | Total n = 2610 ^b |
|---|---------------------|-----------------|-------------------|--|--------------------------------|
| | | 6 mg n = 898 | 12 mg n = 1650 | | |
| Neoplasm SOC TEAEs | 3 (0.2) | 3 (0.3) | 2 (0.1) | | 5 (0.2) |
| Bladder neoplasm | 1 (< 0.1) | 0 | 0 | | 0 |
| Burkitt's lymphoma | 1 (< 0.1) | 0 | 0 | | 0 |
| Carcinoma | 1 (< 0.1) | 0 | 0 | | 0 |
| Chronic myeloid leukemia | 0 | 1 (< 0.1) | 0 | | 1 (< 0.1) |
| Colon cancer metastatic | 0 | 1 (< 0.1) | 0 | | 1 (< 0.1) |
| Hepatic neoplasm | 0 | 0 | 1 (< 0.1) | | 1 (< 0.1) |
| Lymphoma | 0 | 1 (< 0.1) | 0 | | 1 (< 0.1) |
| Thyroid neoplasm | 0 | 0 | 1 (< 0.1) | | 1 (< 0.1) |

^a Patients with > 1 AE in same category counted only once.

^b The 62 patients in the alvimopan 1 mg to 3 mg group are included in the alvimopan total

Patient Follow-up in POI Studies

Worldwide POI Safety Population (N = 3975)

❖ 88% had follow-up

- 75% contacted by telephone after last dose
 - Most at 1 to 2 weeks
- 13% had a follow-up visit (Study 306)

❖ Study 001^a

- Visit 6 weeks following surgery (health outcomes assessment)
- 76% completed

^a In addition to telephone contact at 5 to 7 days after last dose.

Patient Follow-up in POI Studies

Worldwide POI Safety Population

- ❖ Monitoring visits through 30 days after last dose or until resolution for all patients in NA studies
 - BR patients evaluated within 2 to 4 weeks for initial postoperative visit
- ❖ Metabolite concentrations negligible or BLQ at 6 to 11 days post discharge
- ❖ Monitoring period corresponds to time of initial postoperative evaluation

Summary—Safety of Alvimopan for Management of POI in BR Patients

- ❖ Well tolerated
- ❖ No evidence of increased CV risk
 - Clinical safety database
 - Blinded adjudication of patient-level data
- ❖ No evidence of reversal of opioid analgesia
- ❖ Results support a favorable risk profile

Entereg[®] (alvimopan) Proposed Risk Management Plan

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— FDA Requests

❖ Approvable letter 3 November 2006

- “Develop a risk management plan that includes elements to
 - a) communicate the possible cardiovascular risk of longer-term alvimopan exposure and
 - b) minimize off-label use
- This plan could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.”

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan

❖ Primary goal

- Entereg will be indicated for short-term use in inpatient settings
- Entereg will not be used
 - Outside the controlled setting of a hospital
 - Beyond 7 days or 15 doses
 - In opioid-tolerant patients
 - In patients not undergoing bowel resection

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Considerations for Plan Development

- ⌘ POI remains a serious condition with an unmet medical need
- ⌘ No drugs currently approved for the management of POI
- ⌘ Demonstrated clinical benefit in patients undergoing BR
 - Earlier resolution of POI and shortened hospital stay (~ 1 day)
 - Reduced incidence of NG tube insertion
- ⌘ No preclinical or clinical evidence of risk associated with acute (≤ 7 days) use in POI

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Considerations for Plan Development

- ⌘ Single doses of ≥ 3.0 mg in opioid-tolerant patients provoke moderate to severe GI distress
 - Nausea/vomiting
 - Abdominal cramping
 - Diarrhea
- ⌘ Physical/Chemical properties of the hot-melt gelatin capsules
- ⌘ Successful experience with limited distribution agreements
- ⌘ Limit distribution without creating a burdensome process on hospitals and HCPs
- ⌘ Entereg should be easily available to
 - Institutions where BRs are performed
 - HCPs that manage BR patients
 - BR patients as per label

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Components

- ⌘ Limited distribution
- ⌘ Professional labeling
- ⌘ Targeted education
- ⌘ Focused promotion

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Distribution

❖ Limited distribution

- NO samples
- Wholesalers will limit sales to acute-care hospitals
- Wholesalers will place NDC block on retail sales (ie, Entereg will not be a listed ordering option)
- Major pharmacy data systems alert retail pharmacists that Entereg is for hospital use only and contraindicated in opioid-tolerant patients

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Assessment of Limited Distribution

- ❖ Monitor and detect inappropriate distribution
 - Daily reports from wholesalers tracking distribution of product to end-users
 - Tracking sales of Entereg to end-users
- ❖ Immediate corrective action, as needed

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Experience With Limited Distribution

- ❖ Limited distribution agreements are relatively common with specialty products
- ❖ Wholesalers will be contractually required to limit distribution to hospitals only
- ❖ Frequent review of reports
 - Unauthorized shipments identified and corrective action taken immediately with wholesalers
- ❖ Has been successfully used to ensure 99% of sales are made to intended accounts

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Professional Labeling

- ⌘ Myocardial infarctions in OBD Study GSK014 in draft label
- ⌘ Use in BR patients only
- ⌘ Contraindicated in opioid-tolerant patients

ENTEREG is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking ENTEREG. Use of Entereg 12 mg in opioid-tolerant patients results in significant GI adverse effects

- Nausea/vomiting, abdominal cramping, diarrhea
- Information included in Warnings and Precautions

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Professional Labeling

- ⌘ Limited to 7 days or 15 doses
- ⌘ In-hospital use only
 - Reinforced by
 - Highlighting on packaging (box and each individual capsule blister)
 - Highlighted in multiple sections of label

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Targeted Education

- ⌘ All HCPs involved in care of BR patients
 - Key issues
 - BR patients only
 - Contraindicated in opioid-tolerant patients
 - Hospital use only
 - Not to be taken home by patient under any circumstance
 - Limited to 7 days or 15 doses
- ⌘ Continuing training for HCP

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Focused Promotion

- ❖ Directed only to surgeons and hospital-based personnel
 - NO samples
 - Sales force visits to hospital-based outpatient pharmacy reinforcing restriction to inpatient use
- ❖ Advertisements limited to journals associated with HCPs who manage BR patients

Entereg[®] (alvimopan) Capsules Proposed Risk Management Plan— Conclusion

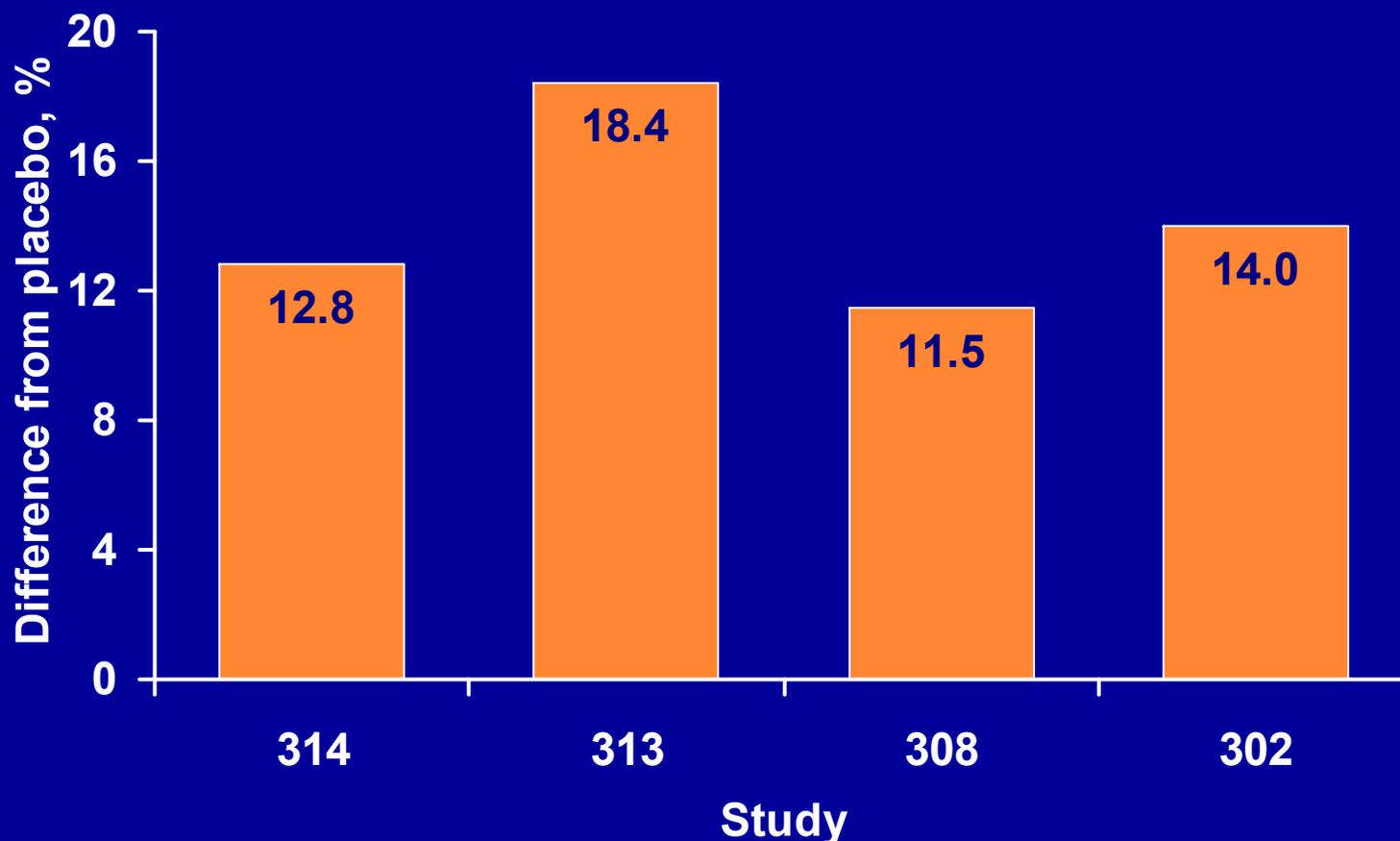
- ⌘ Limited distribution with corrective actions in the event of inappropriate distribution will restrict Entereg to acute-care hospitals
- ⌘ Professional labeling and targeted education to HCPs will reinforce the appropriate use of Entereg
 - Inpatient use
 - Limited to 7 days
 - No more than 15 doses
- ⌘ Result
 - Access to treatment for an unmet medical need
 - Use only in the hospital setting

Entereg[®] (alvimopan)

Summary

Patients Achieving GI-2 Recovery by Postsurgical Day (PSD) 5

Studies 314, 313, 308, 302—BR Only



NNT =

8

5

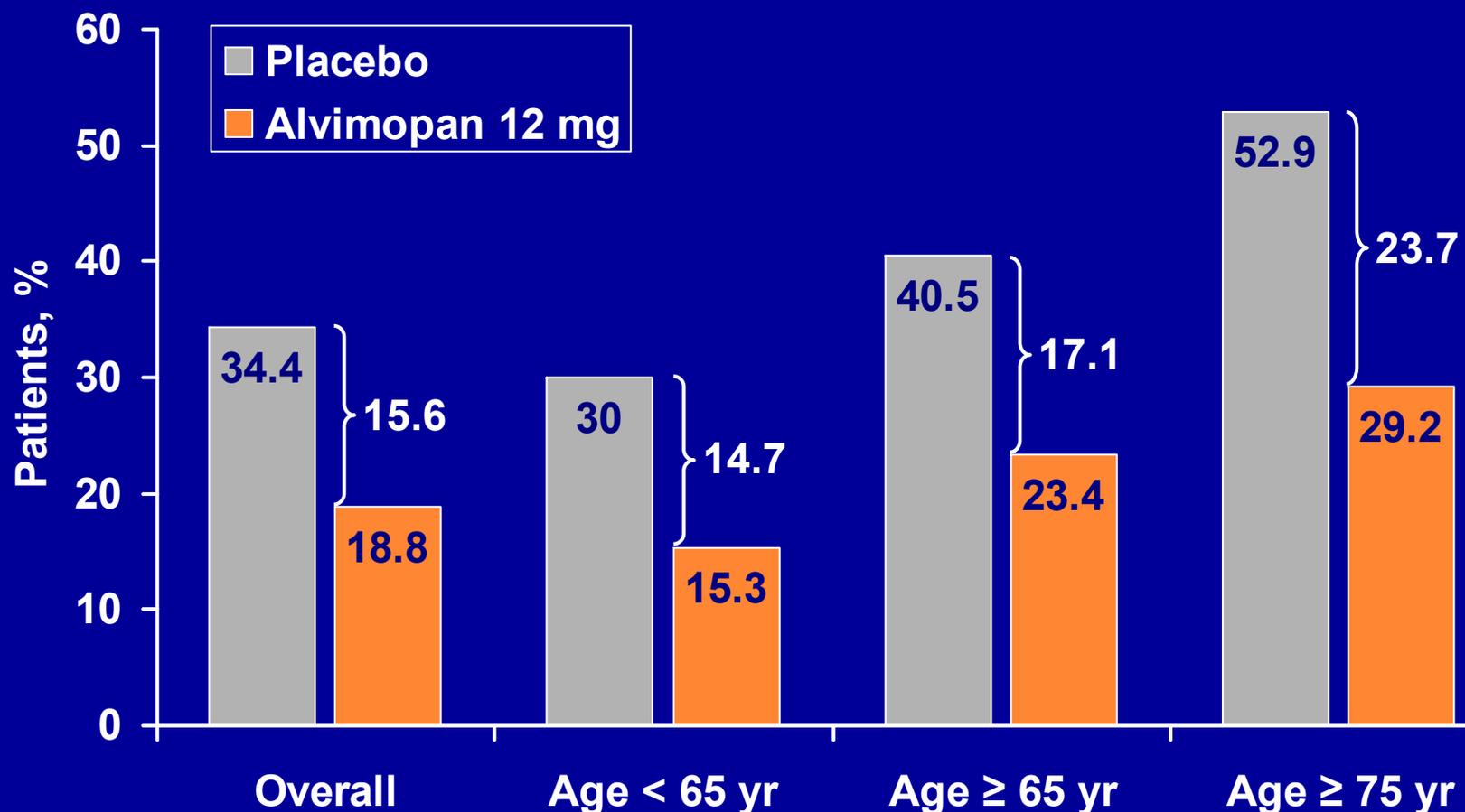
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PSD = Defined in 24-hour intervals from the end of surgery.

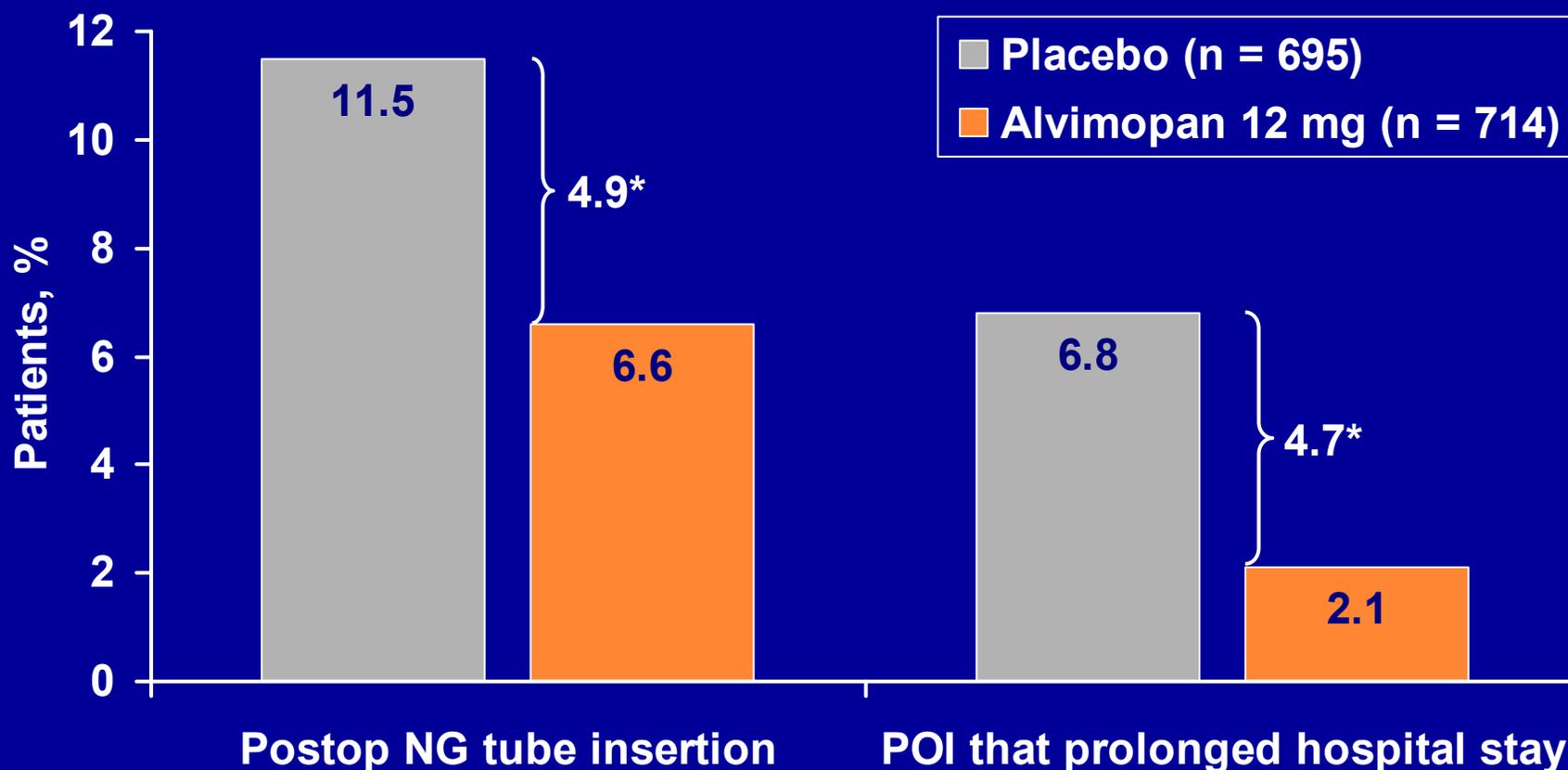
Fewer Patients With Prolonged Hospital Stay—DOW ≥ 7 PODs

Pooled Studies 314, 313, 308, 302—BR Only



Reduced Need for Intervention or Change in Hospital Management

Pooled Studies 314, 313, 308, 302—BR Only



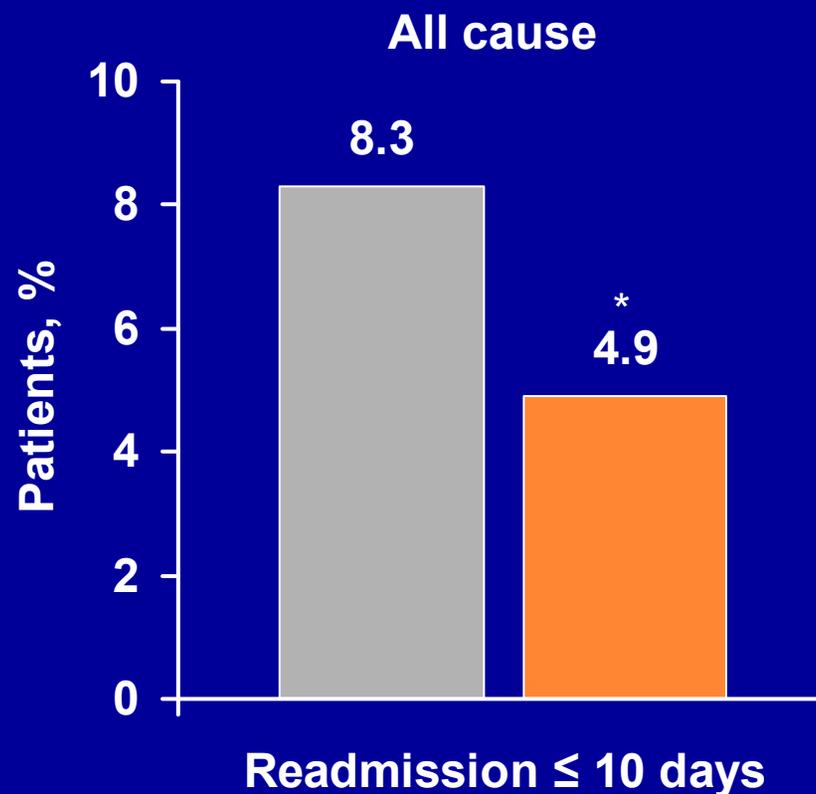
Adapted from Wolff BG, et al. *JACS*. 2007;204:609-616.

* $p < 0.001$

Hospital Readmission

Pooled Studies 314, 313, 308, 302—BR only

■ Placebo ■ Alvimopan 12 mg



* $p < 0.05$

Entereg[®] Overall Summary

- ⌘ No safety issues identified in POI population**
- ⌘ Numerical imbalances in SAEs in OBD were unprecedented and principally isolated to GSK014**
- ⌘ Proposed Risk Management Plan will limit the drug to the hospital setting only**
- ⌘ Alvimopan represents a favorable and compelling benefit/risk profile in POI**

Proposed Indication

- ❖ **ENTEREG[®] (alvimopan) is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis**