Entereg® (alvimopan) Capsules Clinical Development Program and Efficacy

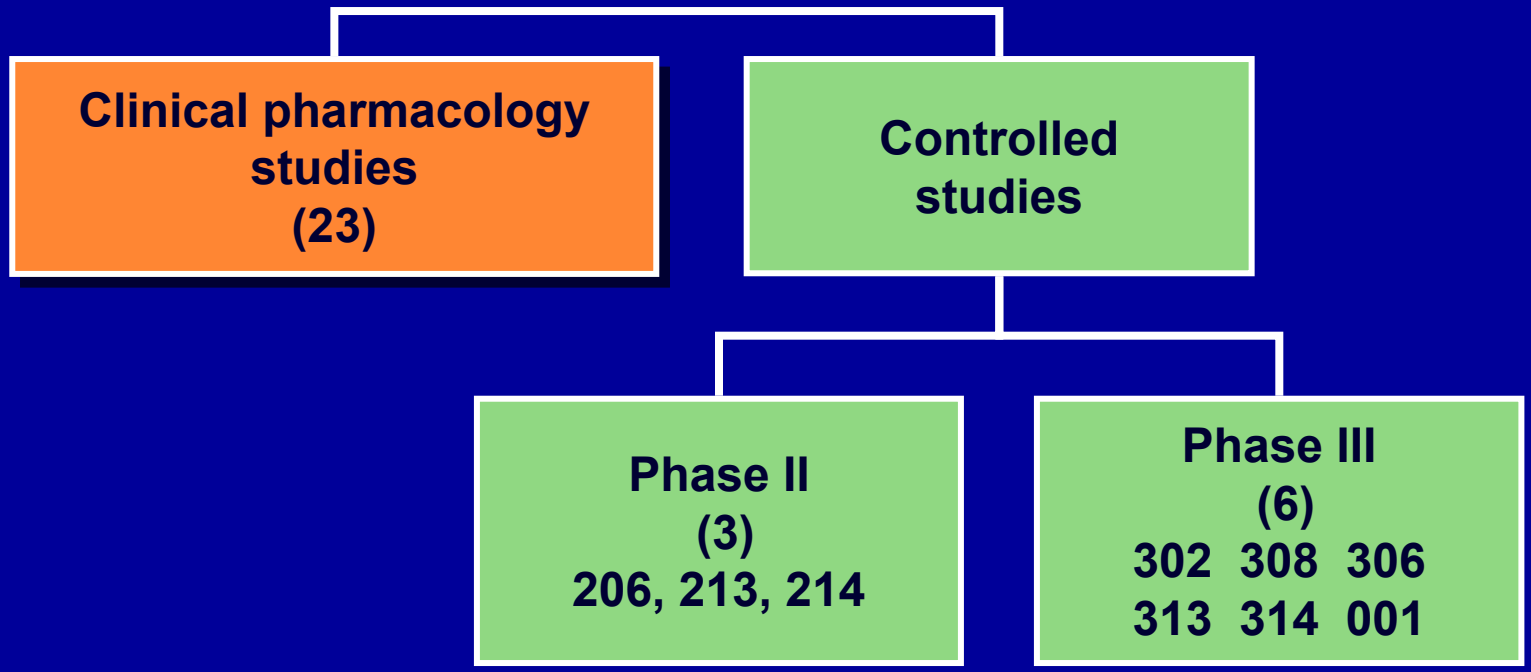
Lee Techner, DPM

Senior Medical Director
Adolor Corporation

Presentation Outline

- Mechanism of action
- Phase III clinical trials
  - Study design
  - Endpoints
- Phase III efficacy results
  - GI recovery
  - Hospital length of stay
  - Postoperative NG tube insertion
  - Opioid consumption and pain scores
- Summary

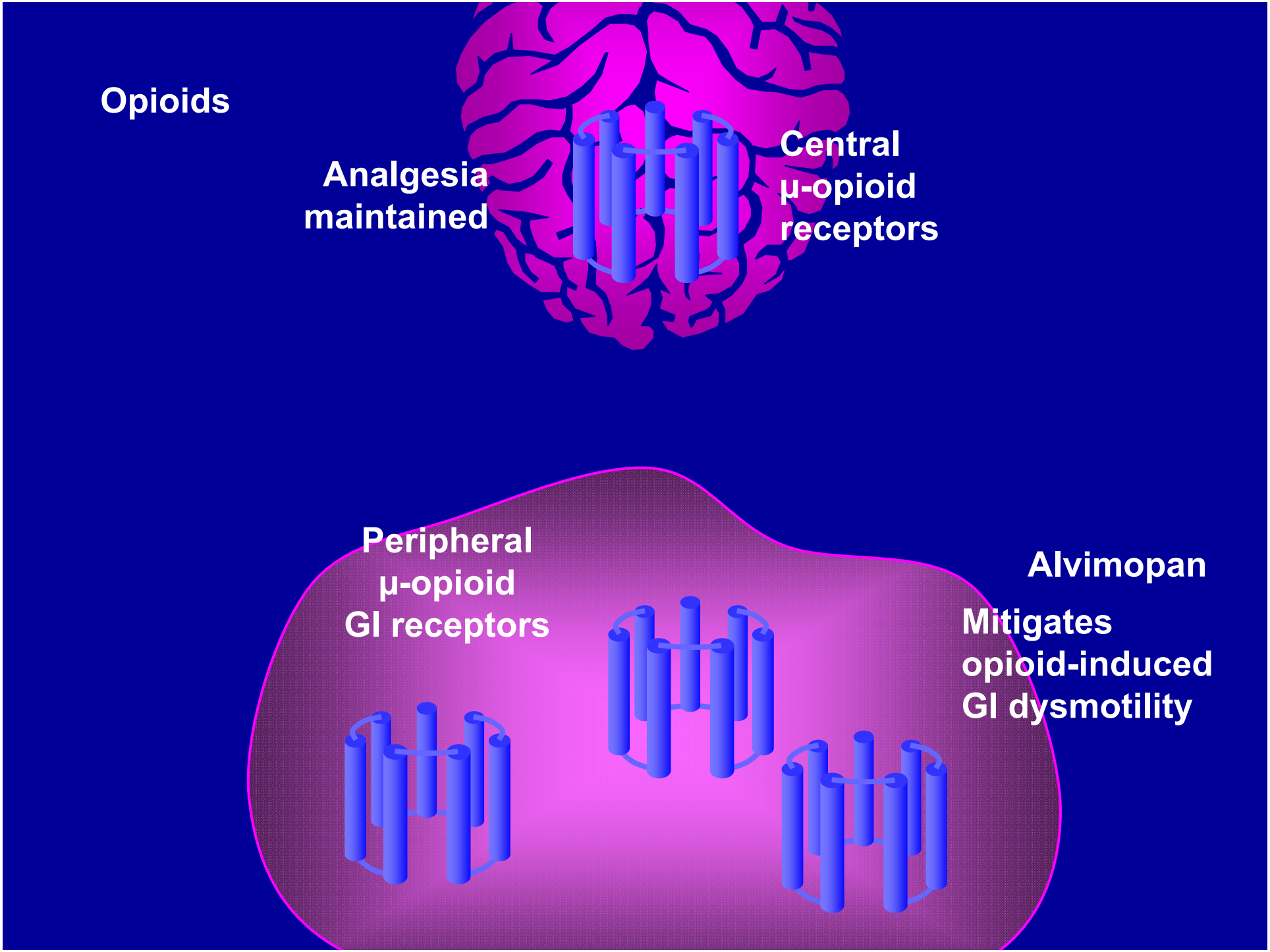
Alvimopan POI Clinical Development Program



Entereg® (alvimopan)

- Selective and competitive antagonist at μ-opioid receptor
- Metabolized to active metabolite by gut microflora
- Peripherally acting

	K_i, nM	
Receptor	Alvimopan	Metabolite
μ	0.44	0.81
δ	10	110
κ	100	290

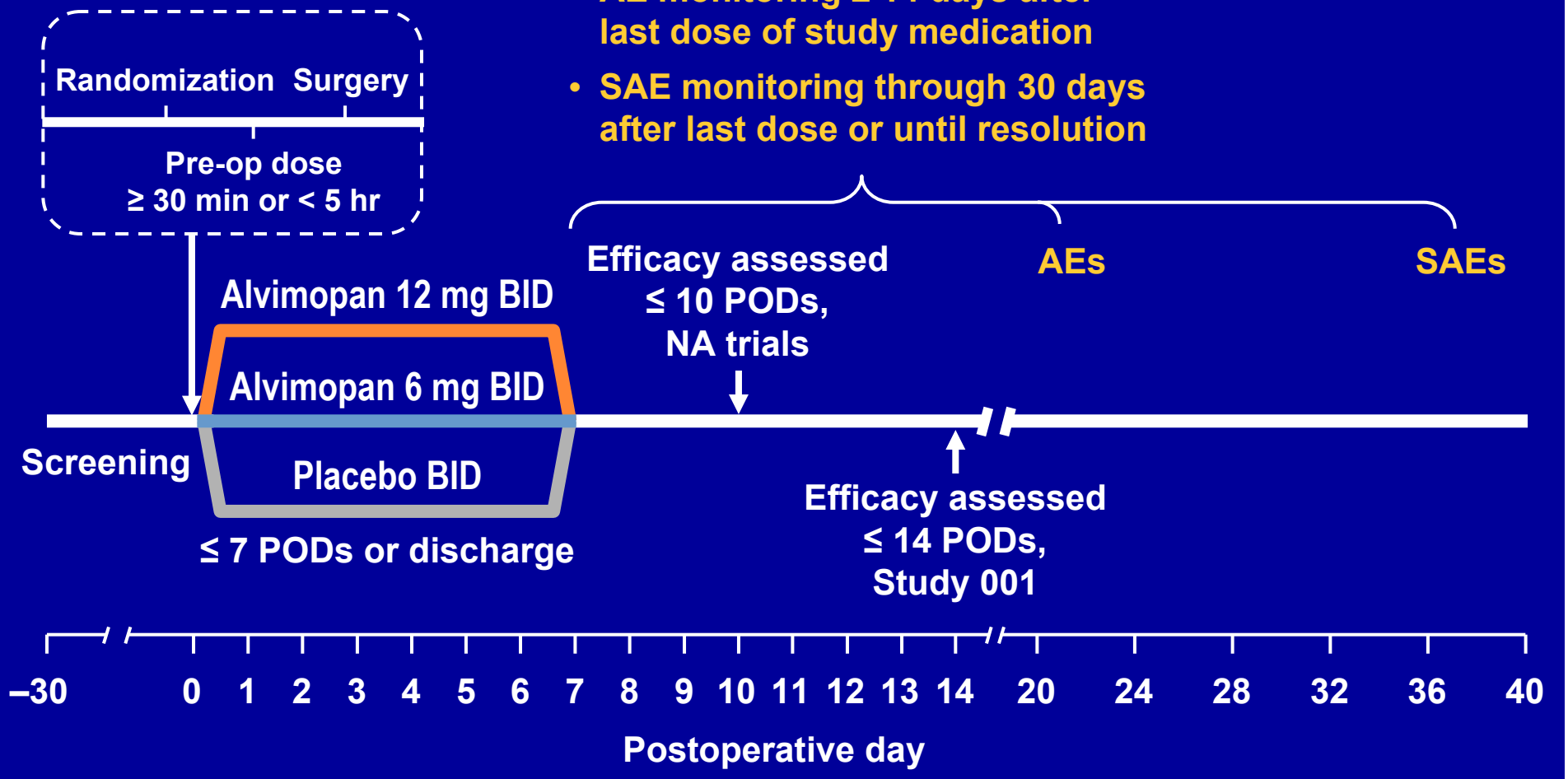

Opioids
Analgesia maintained
Central μ-opioid receptors
Peripheral μ-opioid GI receptors
Alvimopan
Mitigates opioid-induced GI dysmotility

Presentation Outline

- Mechanism of action
- Phase III clinical trials
- Phase III efficacy results
- Summary

Phase III Study Design

- AE monitoring ≤ 14 days after last dose of study medication
- SAE monitoring through 30 days after last dose or until resolution



POD = Postoperative day; defined in 24-hour intervals based on the calender day.

Dose Selection

- Evaluated 1 mg to 12 mg in dose-ranging studies
  - 6 mg and 12 mg chosen for initial phase III trials
- Population PK analysis supports 12-mg BID dosing
  - Concentrations of 12 mg above K_i for mu-opioid receptor 2 × longer than 6-mg dose
- Clinical trial results support 12 mg
- Well tolerated, no increased risk over 6-mg dose

Standardized Accelerated Multimodal Postoperative Care Pathway

- Early NG tube removal
- Early ambulation
  - Initiated POD 1
- Early diet advancement
  - Liquids offered on POD 1
  - Solids offered on POD 2

Key Inclusion Criteria

- ASA score of I - III
- Partial small or large bowel resection with primary anastomosis or TAH performed by laparotomy
- Postoperative pain management with opioid-based IV patient-controlled analgesia (PCA)

Key Exclusion Criteria

- Total colectomy, colostomy, ileostomy
- Complete bowel obstruction
- Chronic opioid use
- More than 3 doses of opioid analgesics within 7 days prior to surgery

Demonstration of Clinically Meaningful Benefit

- GI recovery[a]
  - Primary measure of clinical progress
  - Driver for decisions around discharge
- Hospital length of stay[a]
- Postoperative nasogastric (NG) tube insertion

[a] End of surgery time used as reference point.

Endpoint Selection
Primary Endpoints—GI Recovery

- GI-3 (initial phase III studies; BR and TAH)
  - Upper GI recovery: time to tolerating solid food
  - Lower GI recovery: first to occur of either bowel movement (BM) or flatus
- GI-2 (Study 314; BR only)
  - Upper GI recovery: time to tolerating solid food
  - Lower GI recovery: time to first BM
    - Prespecified secondary endpoint in 3 studies (313, 308, 001)
    - Post hoc analysis in 1 study (302)

Endpoints for Assessment of Hospital Length of Stay

- Ready for discharge based solely on GI recovery as defined by the surgeon
- Time to discharge order written (DOW)
- Postoperative length of stay (LOS)
  - DOW by postoperative day (POD)

POD = Defined in 24-hour intervals based on the calender day.

(0423) Source:

Responder Analysis

- Prespecified in most recent trial
  - Retrospective analysis for initial NA studies
- Definition
  - Endpoint achieved on postsurgical day (PSD) 3 to 8
  - No subsequent AE reports of POI that according to investigator
    - Delayed discharge
    - Resulted in readmission within 7 days

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

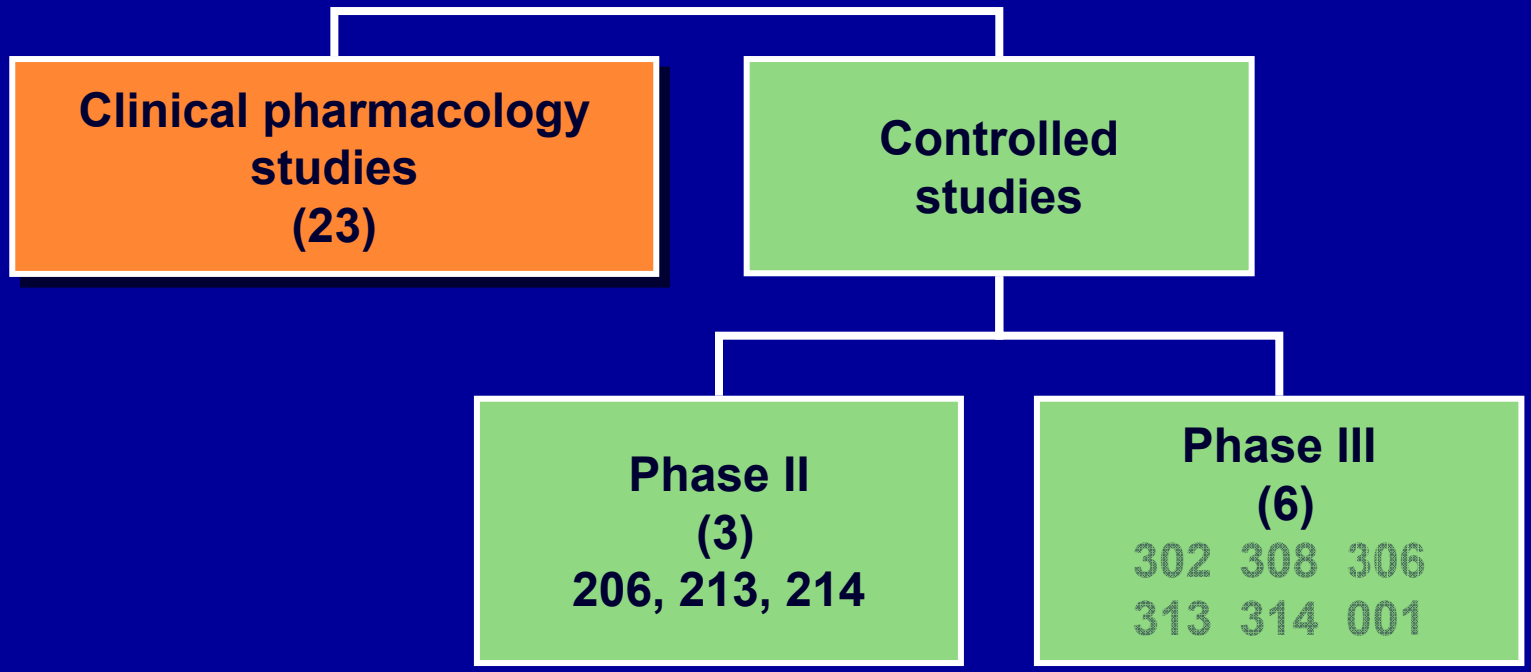
Key GI Recovery and Discharge Milestones

- Proportion of responders
  - GI recovery by PSD 5
  - DOW prior to PSD 7

Presentation Outline

- Mechanism of action
- Phase III clinical trials
- Phase III efficacy results
- Summary

Efficacy Presentation
Phase III Studies



- Patients who underwent BR
- Patients who received placebo or alvimopan 12 mg

Statistical Analysis Populations

- Modified intent-to-treat (MITT)
  - All patients who had
    - At least 1 dose of study drug,
    - Protocol-specified surgery (segmental BR)
    - At least 1 post-surgery efficacy assessment
- In NA trials 94% of BR patients included in BR MITT

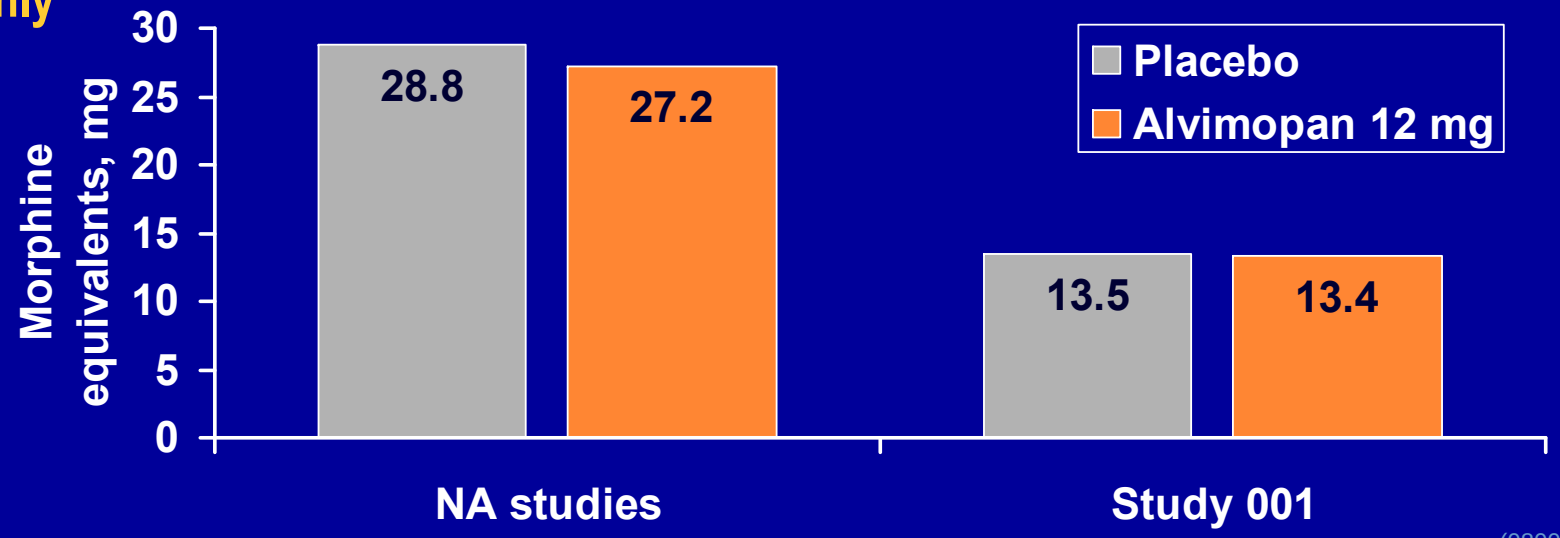
Analyses Supporting Clinical Benefit

- Hazard ratio (Cox proportional hazards)
  - Treatment effect (*p* value)
- Mean (KM AUC), median, 75th percentile
  - Magnitude of treatment effect
- Proportion of responders
- NNT (reciprocal of absolute difference in proportion of responders)

Differences Between North American Studies and Study 001

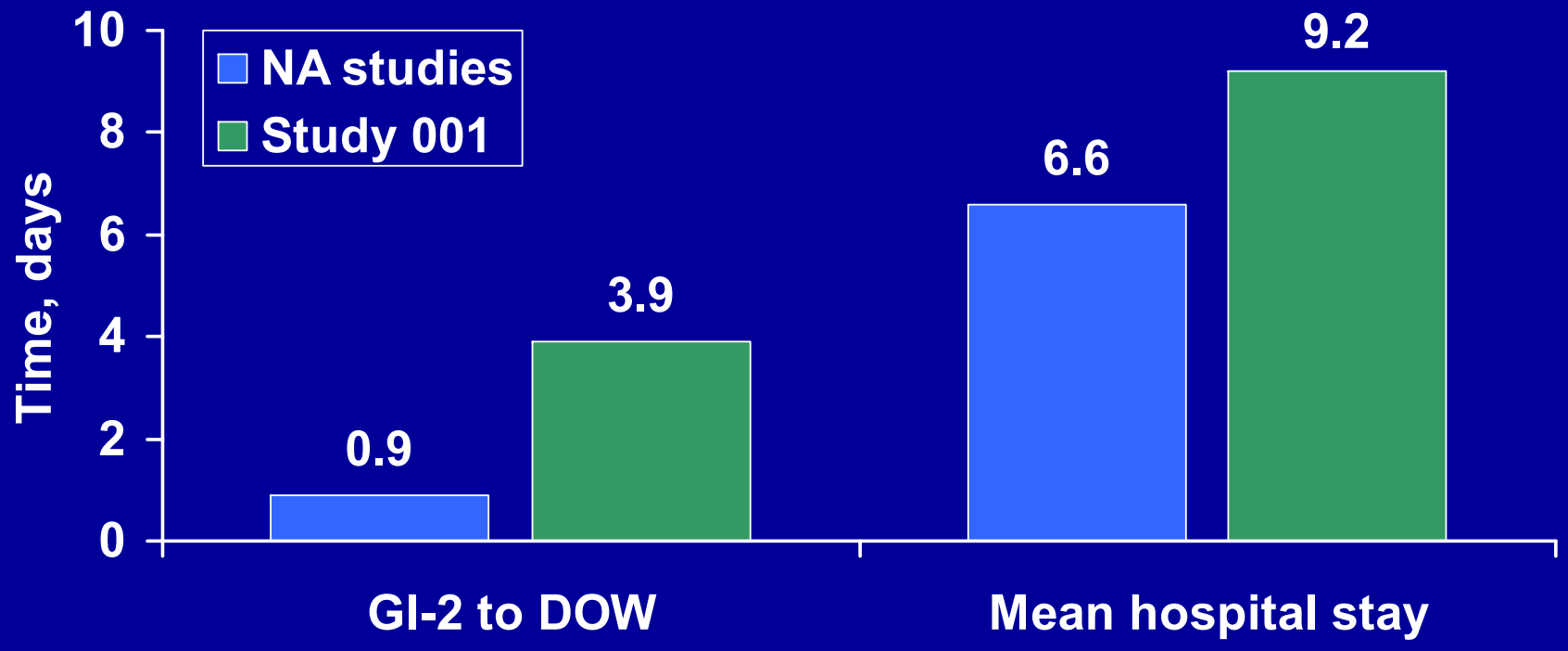
All patients	North American studies	Study 001
Route of opioid administration	IV PCA only	IV PCA or bolus parenteral
Use of ketorolac or other non-opioid analgesics	Restricted < 4% of patients	Not restricted 69% of patients
Extent of IV PCA use	99% of patients	45% of patients

BR only



Differences[a] Between North American Studies and Study 001

- GI recovery not a primary determinant of discharge in Study 001



[a] Placebo BR population – difference in KM means.

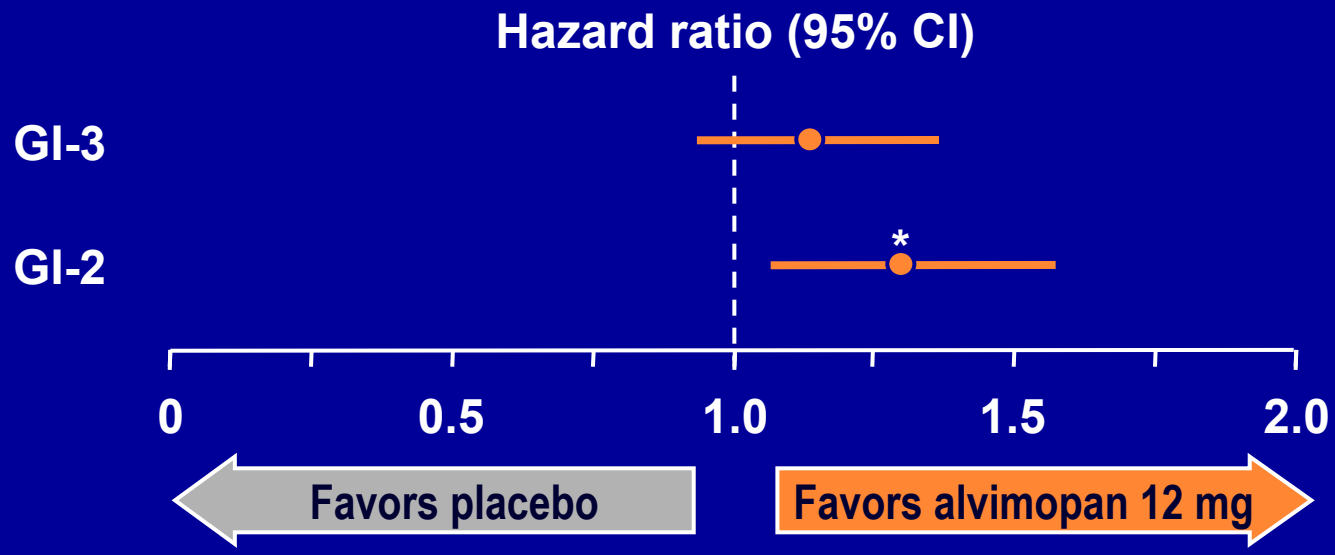
Baseline Surgical Characteristics
Study 001—BR Only

	Placebo n = 229	Alvimopan 12 mg n = 239
Mean age (SD), yr	63.8 (12.04)	64.0 (13.21)
Female, %	45.4	44.4
Mean BMI (SD), kg/m^2	26.7 (4.61)	26.4 (4.39)
Primary reason for surgery malignancy, %	72.5	78.2
Mean overall surgery duration (SD), hr	2.6 (1.02)	2.6 (1.10)

Patient Disposition
Study 001—BR Only

Characteristic	Patients, %	
	Placebo n = 229	Alvimopan 12 mg n = 239
Completed treatment	77.7	82.4
Discontinued due to AEs	3.1	4.6
Discontinued due to other	19.2	13.0

Time to GI Recovery
Study 001—BR Only



	Difference from placebo, hr	
Quartile	GI-3	GI-2
Mean (95% CI)	4.8 (–2.6, 12.2)	10.6 (2.7, 18.5)
Median	3.2	3.1
75th percentile	4.4	20.3

*Statistically significant at 0.05 level using Hochberg method for 2-dose comparisons, where applicable.

Phase III POI Efficacy Studies Population Overview

Trial	Patients, N	Patients, n (%)	
		BR	TAH
314	654	654 (100)	—
313	510	472 (93)	25 (5)
308	665	437 (66)	200 (30)
302	449	303 (68)	129 (29)
Total[a]	2278	1866 (82)	354 (16)
001[b]	911	705 (77)	206 (23)

Study 306 (not listed) was a phase III safety study in patients undergoing TAH (n = 519).

[a] Safety population: includes 6 mg and 12 mg treatment groups.

[b] Non-US Study.

(0412) CSRs: 314 T 7; 313 T 12; 308 T 12; 302 T 13; 001 § 3.1

Patient Disposition
Studies 314, 313, 308, 302—BR Only

Characteristic	Study 314		Study 313		Study 308		Study 302	
	Pla	Alv 12 mg	Pla	Alv 12 mg	Pla	Alv 12 mg	Pla	Alv 12 mg
Total patients, n	312	317	142	160	142	139	99	98
Completed treatment, %	81.1	83.9	76.8	85.0	79.6	86.3	82.8	75.5
Discontinued due to AEs, %	13.8	9.8	17.6	8.8	17.6	10.1	15.2	20.4
Discontinued due to other, %	5.1	6.3	5.6	6.3	2.8	3.6	2.0	4.1

(04130) Source: ISE T 4; 001 suppl T1.2

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

Characteristic	Placebo n = 695	Alvimopan 12 mg n = 714
Mean age (SD), yr	60.4 (14.13)	60.7 (14.58)
Age ≥ 65 yr, %	41.9	43.1
Age ≥ 75 yr, %	17.1	16.8
Race, %		
White	84.7	83.9
Other	15.3	16.1
Female, %	52.1	50.1
Mean BMI (SD), kg/m^2	28.5 (6.20)	27.7 (6.00)

(04101) Source: ISE2 T 2.2, 3.2

Baseline Surgical Characteristics
Pooled Studies 314, 313, 308, 302—BR Only

Characteristic	Placebo n = 695	Alvimopan 12 mg n = 714
Surgery, %		
Small BR	7.2	9.1
Large BR	92.8	90.9
Left	56.3	53.8
Right	36.5	37.1
Mean overall duration (SD), hr	2.2 (1.12)	2.1 (1.12)

(04104) Source: ISE2 T 2.2, 3.2

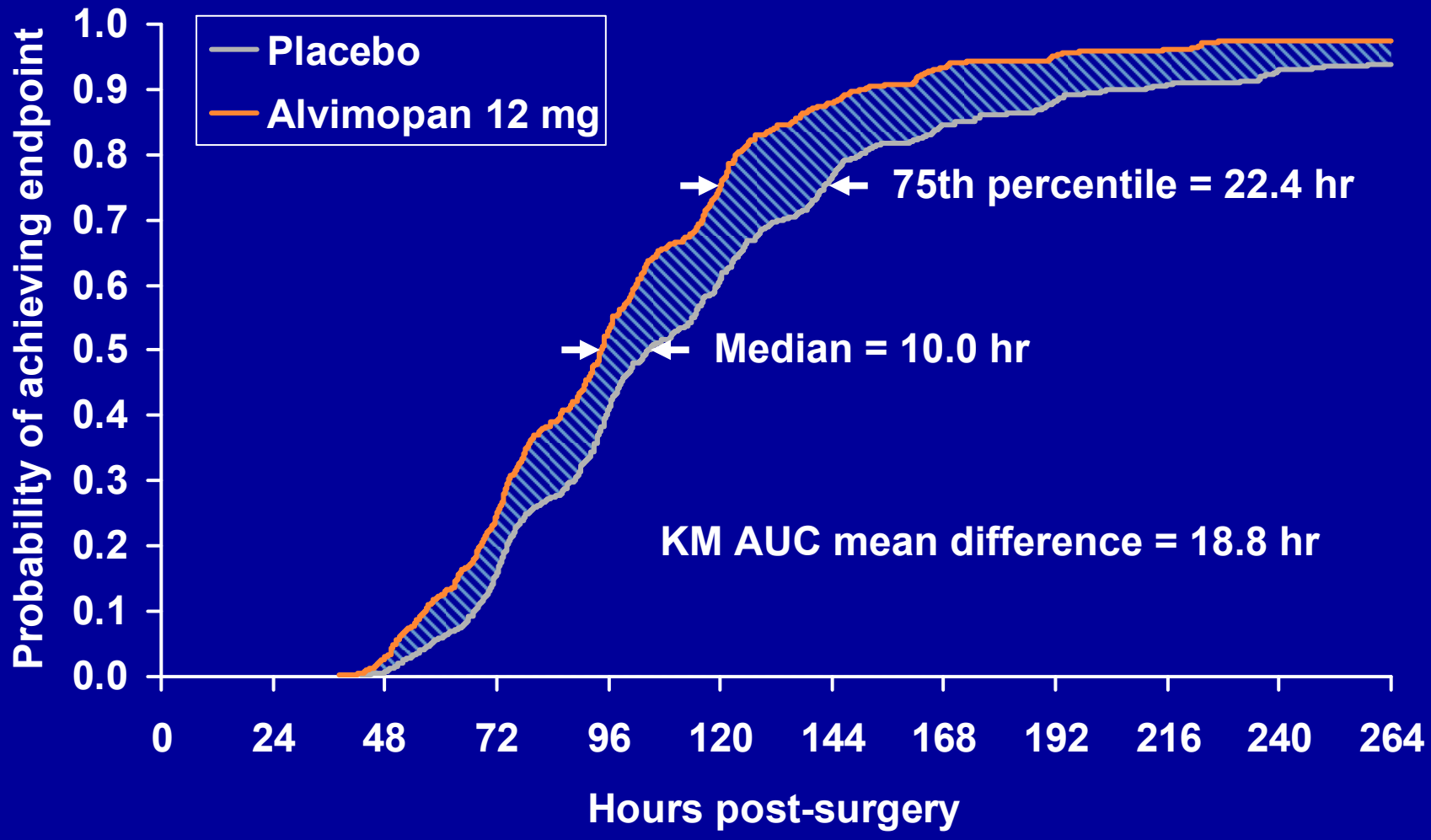
Primary Indication for Surgery
Pooled Studies 314, 313, 308, 302—BR Only

Primary reason for surgery	Patients, %	
	Placebo n = 695	Alvimopan 12 mg n = 714
Colon/rectal cancer	50.2	52.4
Diverticular disease	16.4	15.3
Ostomy reversal	8.9	10.2
Intestinal polyps	9.4	7.8
Crohn's disease	5.0	6.9
Other[a]	10.1	7.4

[a] Includes rectal prolapse, intestinal fistula, small bowel cancer.

Acceleration of GI-2 Recovery—KM Estimates

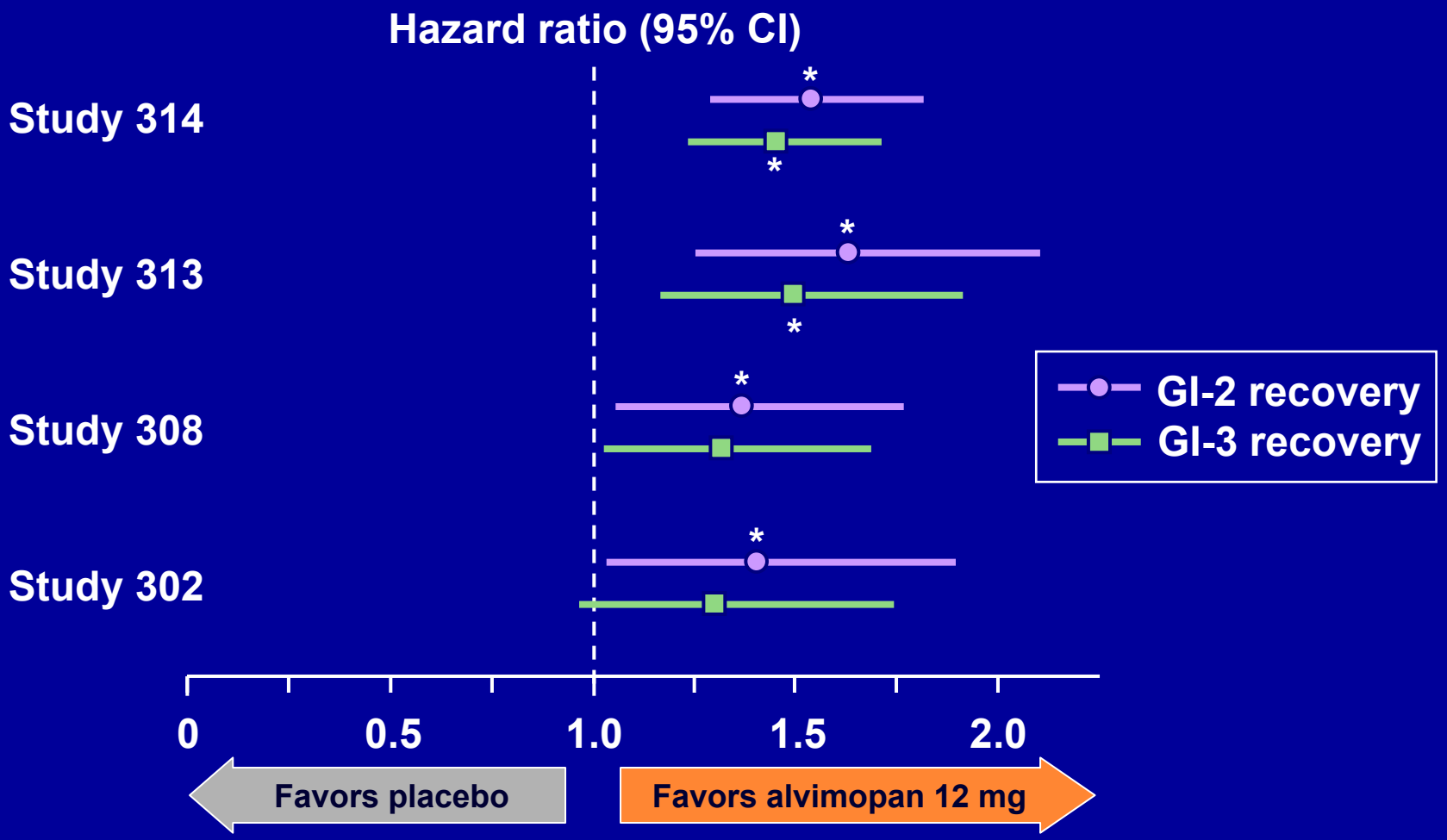
Pooled Studies 314, 313, 308, 302—BR Only



(04148) Source: CSR Fig 27.1

Hazard Ratios for Treatment Effect—GI Recovery

Studies 314, 313, 308, 302—BR Only



*Statistically significant at 0.05 level using Hochberg method for 2-dose comparisons, where applicable.

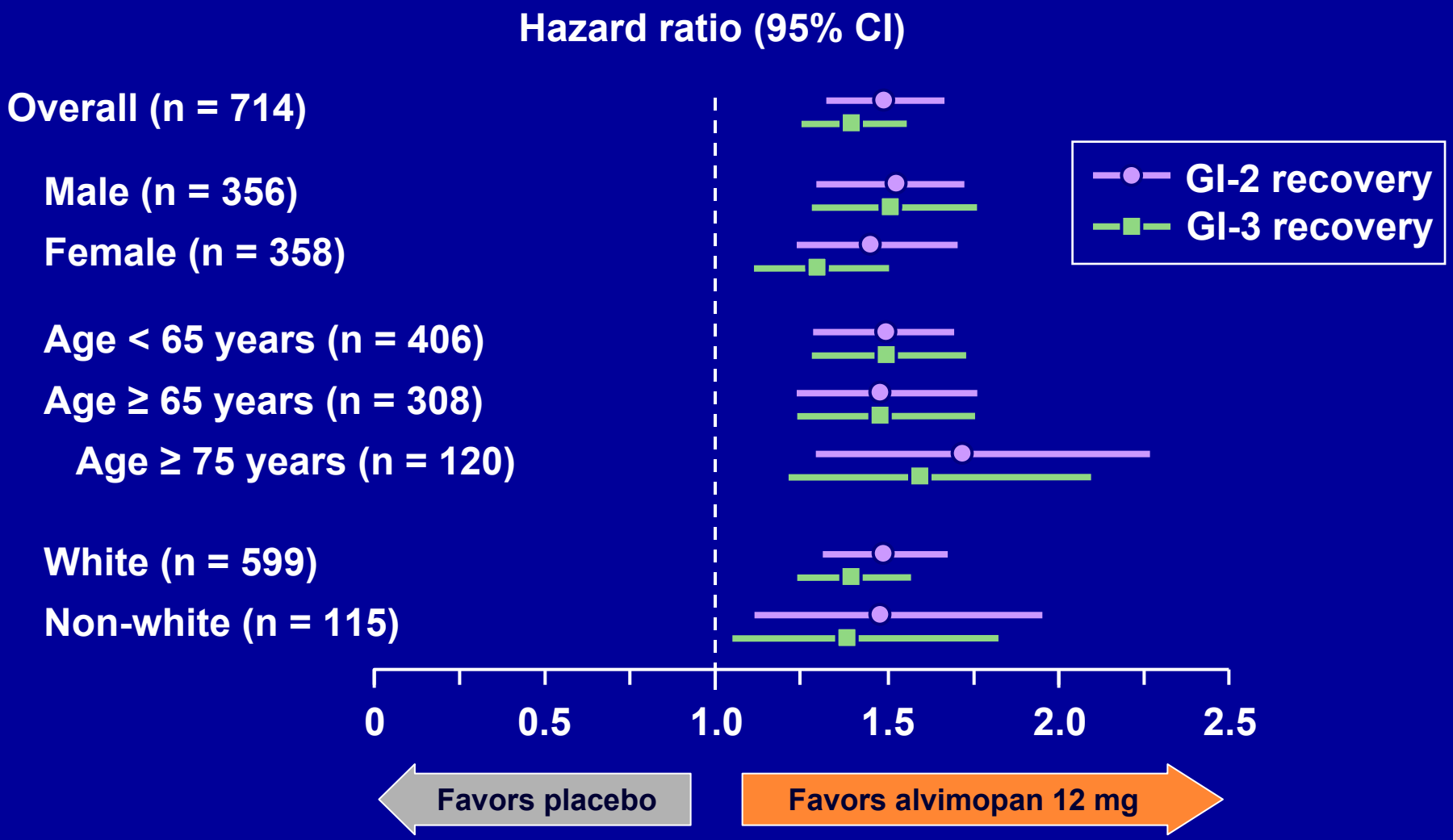
(04131) Source: ISE T 5.2.2.1, 5.2.2.2, 5.2.2.3; 314 CSR T 14.2.1.1.1; 001 suppl T 2.1

KM Estimates for Magnitude of Treatment Effect—GI Recovery
Studies 314, 313, 308, 302—BR Only

	Difference from placebo, hr			
Endpoint	Study 314	Study 313	Study 308	Study 302
GI-2 recovery				
Mean (95% CI)	19.8 (11.9, 27.6)	26.1 (12.5, 39.7)	14.0 (0.7, 27.2)	13.2 (1.2, 25.2)
Median	16.6	17.2	15.0	11.9
75th percentile	20.2	39.4	25.2	22.2
GI-3 recovery				
Mean (95% CI)	15.8 (8.9, 22.6)	20.2 (7.4, 32.9)	12.4 (0.1, 24.7)	10.3 (–1.7, 22.3)
Median	9.1	4.8	11.8	10.8
75th percentile	15.1	21.9	23.5	19.6

(04132) Source: ISE T 6.2.1, 6.2.2, 6.2.3; 314 CSR T 14.2.1.2.1

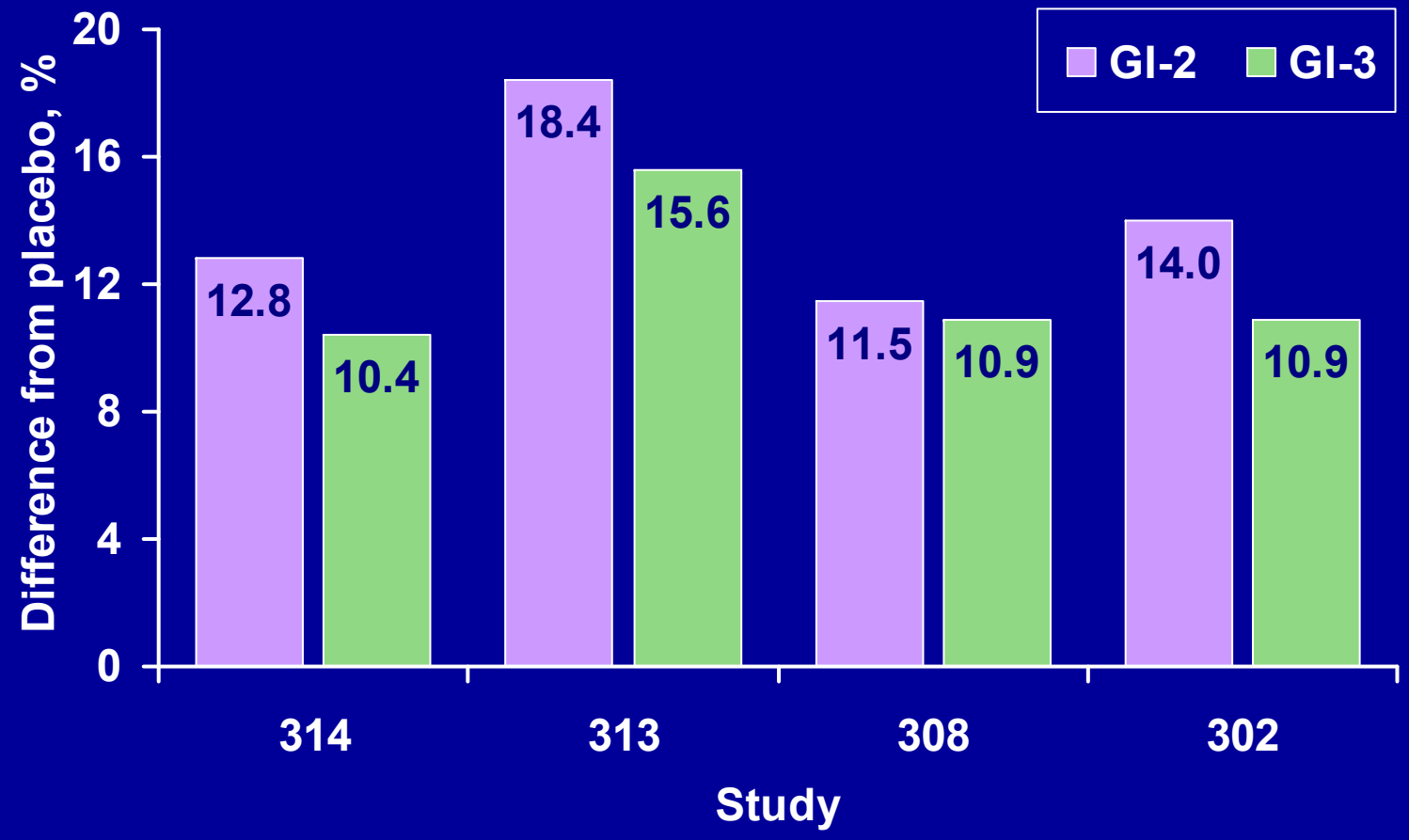
Subgroups GI-2 and GI-3 Analyses
Pooled Studies 314, 313, 308, 302—BR Only



(0464) Source: T 5.2.1.2, 5.2.3.2, 5.2.4.2, 5.2.5.2, 5.2.6.2

Patients Achieving GI-2 and GI-3 Recovery by Postsurgical Day (PSD) 5

Studies 314, 313, 308, 302—BR Only

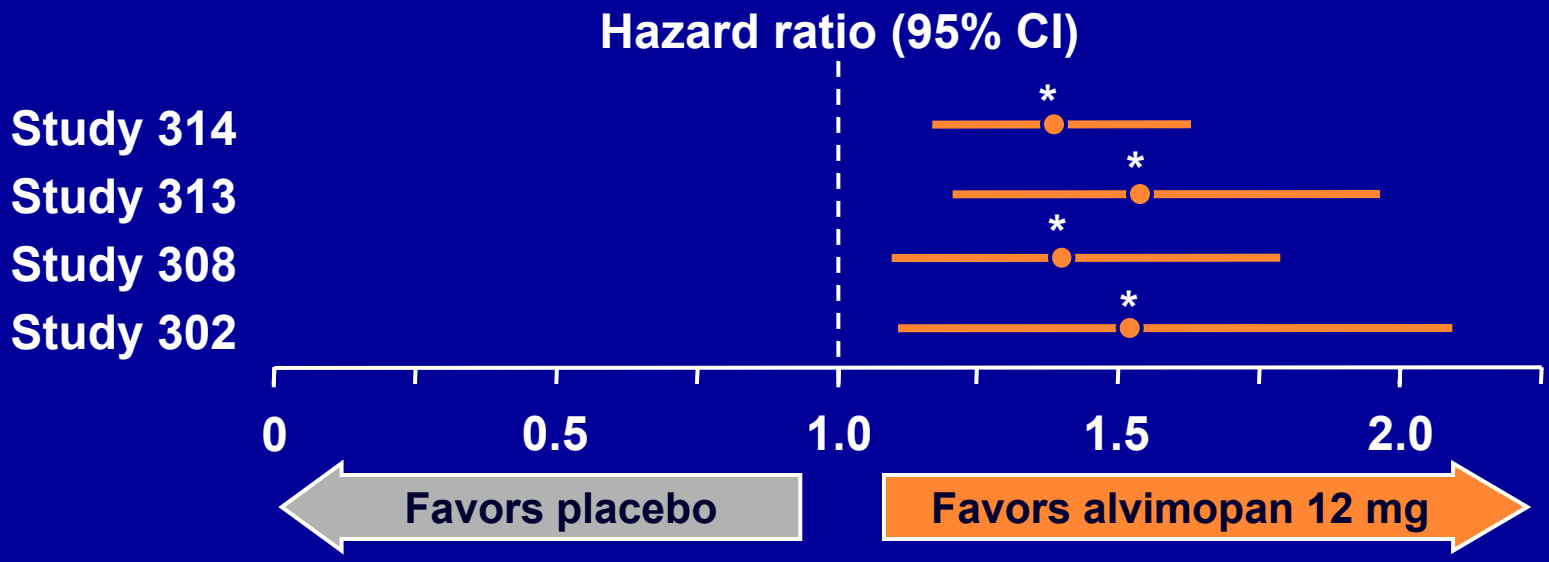


NNT =	8	10	5	6	9	9	7	9

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

(0465) Source: ISE T 7.3, 7.4, 7.5; 314 CSR T 14.2.1

Ready for Discharge
Studies 314, 313, 308, 302—BR Only



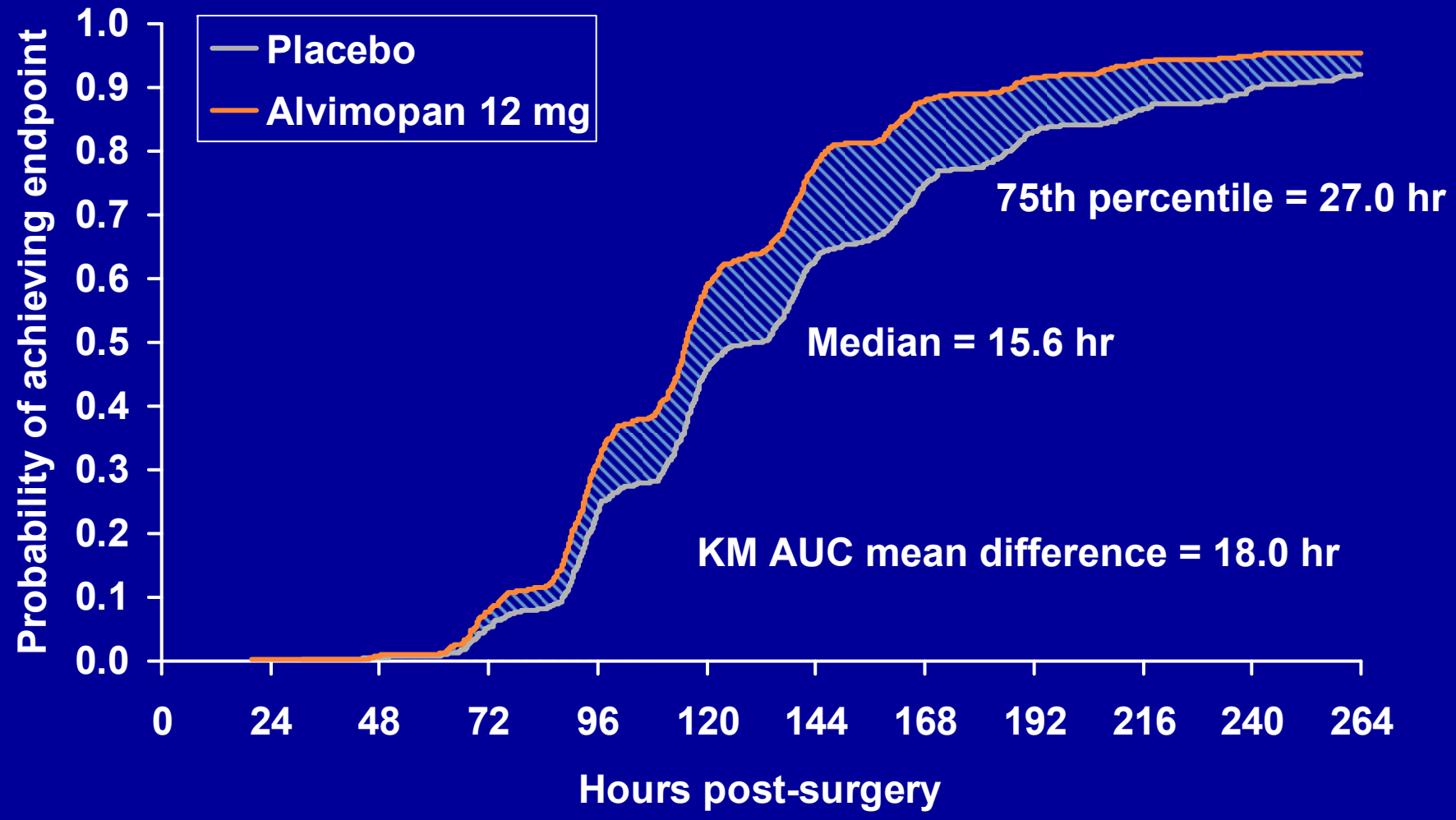
Difference from placebo, hr	Study 314	Study 313	Study 308	Study 302
Mean (95% CI)	13.1 (6.1, 20.1)	20.9 (8.6, 33.1)	14.7 (3.3, 26.2)	16.4 (4.3, 28.4)
Median	10.6	16.1	11.5	13.5
75th percentile	21.1	24.5	21.7	19.4

*Statistically significant at 0.05 level using Hochberg method for 2-dose comparisons, where applicable.

(0480) Source: 314 CSR T 14.2.1.1.1; ISE T 5.2.2.3, 5.2.2.2, 5.2.2.1
314 CSR T 12; ISE T 6.2.3, 6.2.2, 6.2.1

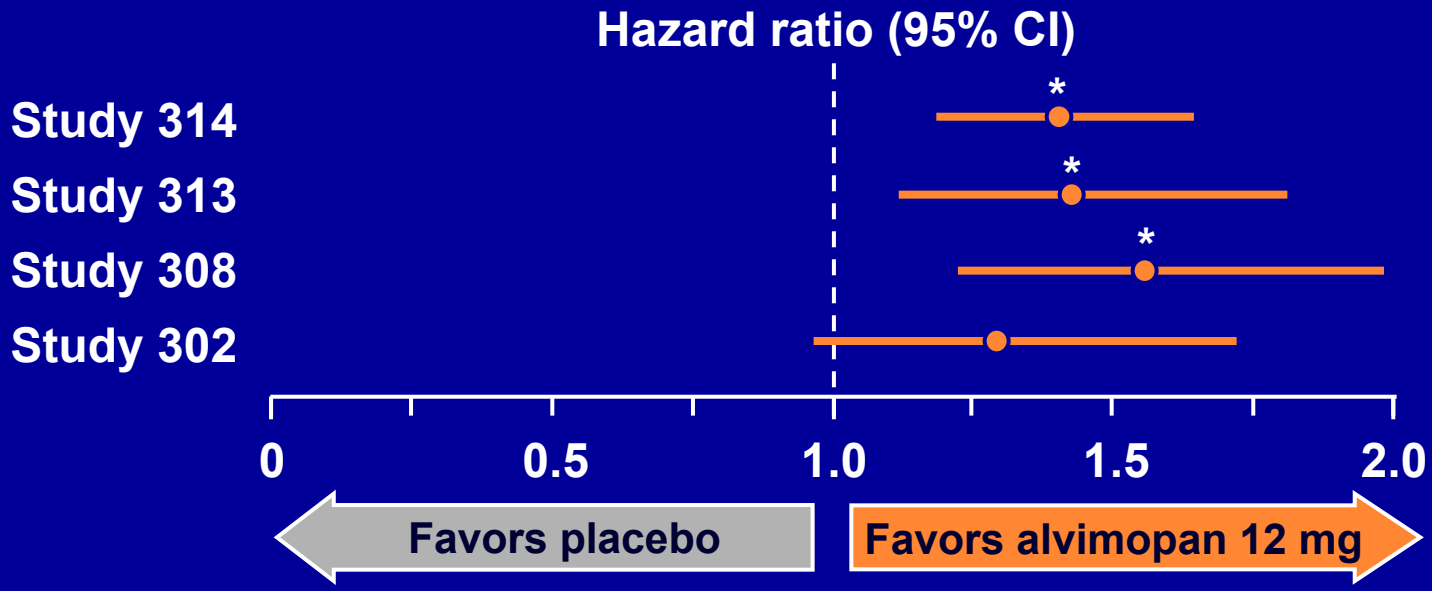
DOW—KM Estimates

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



(04149) Source: CSR Fig 27.2

Hospital DOW
Studies 314, 313, 308, 302—BR Only

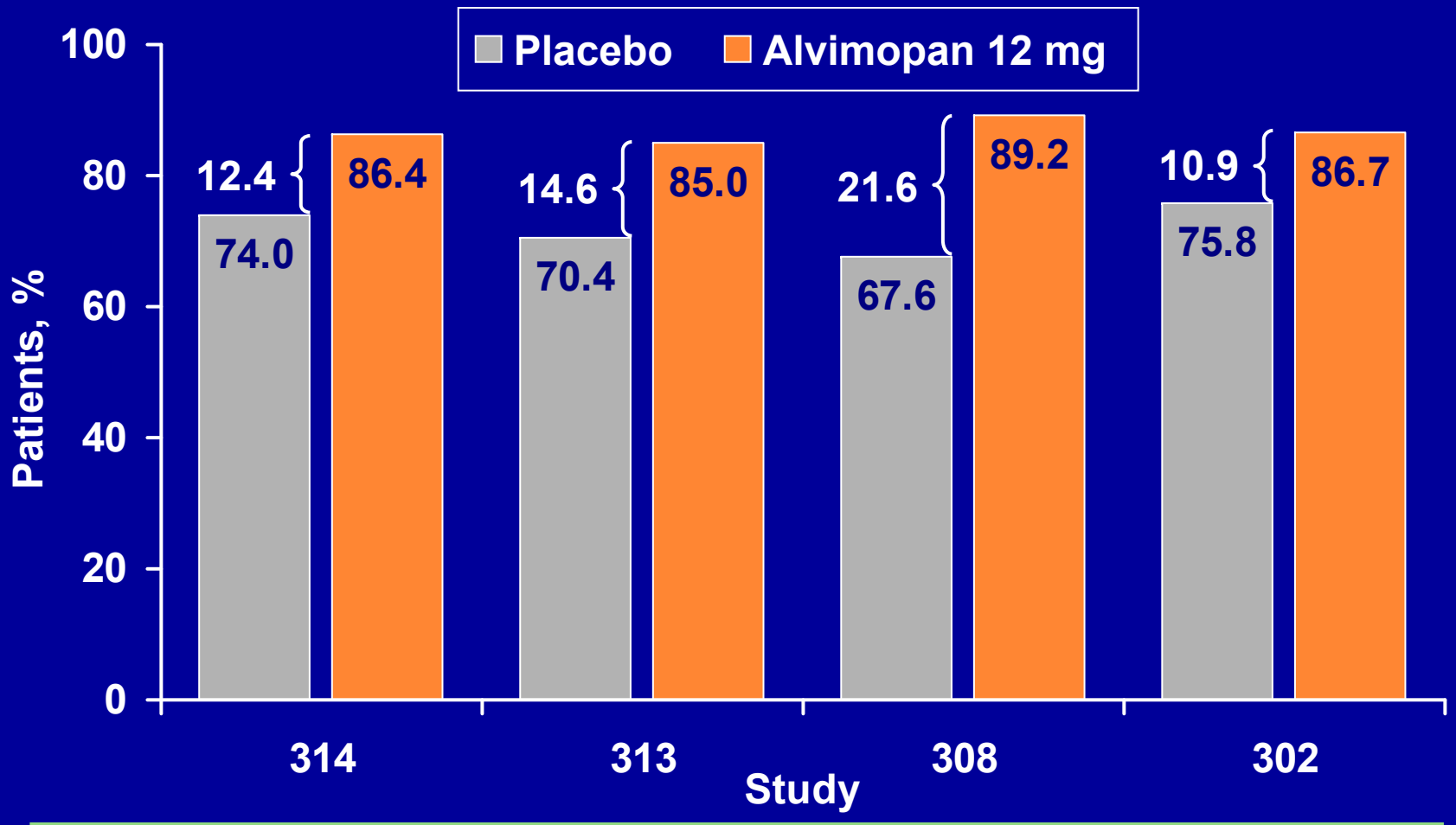


Difference from placebo, hr	Study 314	Study 313	Study 308	Study 302
Mean (95% CI)	17.6 (9.4, 25.8)	19.3 (6.3, 32.2)	21.3 (10.2, 32.4)	12.9 (0.3, 25.5)
Median	7.8	6.0	22.3	16.3
75th percentile	25.2	44.9	43.2	21.1

*Statistically significant at 0.05 level using Hochberg method for 2-dose comparisons, where applicable.

(0466) Source: ISE T 5.2.2.1, 5.2.2.2, 5.2.2.3; 314 CSR T 14.2.1.1
ISE T 6.2.1, 6.2.2, 6.2.3; 314 CSR T 14.2.1.2

Hospital DOW < PSD 7
Studies 314, 313, 308, 302—BR Only



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

(0467) Source: CSR 314 T 14.2.1.5; ISE2 T 7.5, 7.4, 7.3,

Mean Postoperative Length of Stay[a] (Days)
Studies 314, 313, 308, 302—BR Only

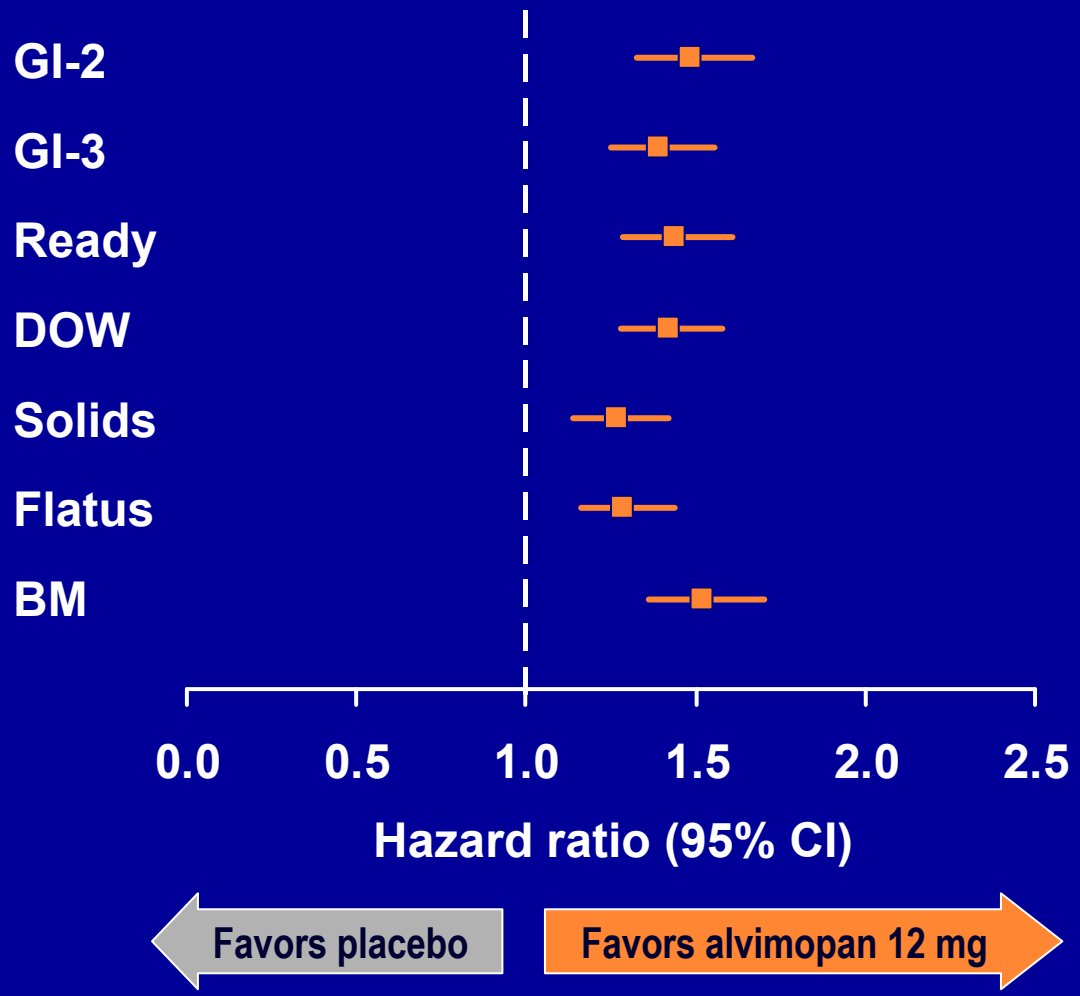
Study	Placebo	Alvimopan 12 mg	Difference
314	6.2	5.2	1.0
313	7.4	6.1	1.3
308	6.6	5.7	0.9
302	6.4	6.1	0.3

[a]Based on calendar day of DOW; day of surgery = day 0

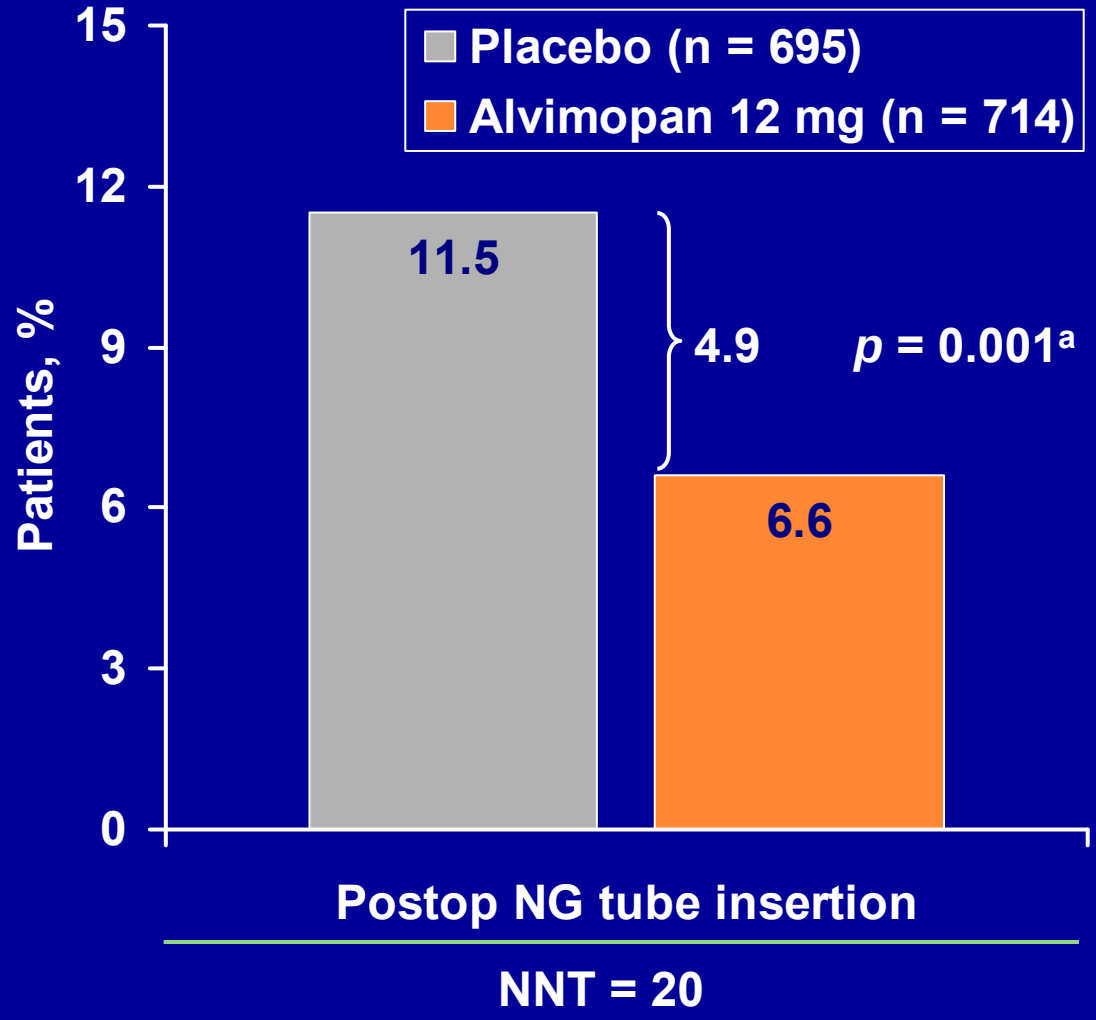
(04133) Source: T 8.2, 8.3, 8.4; 314 CSR T 14.2.9.1

Hazard Ratios (95% CI) for Time to Event Endpoints

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

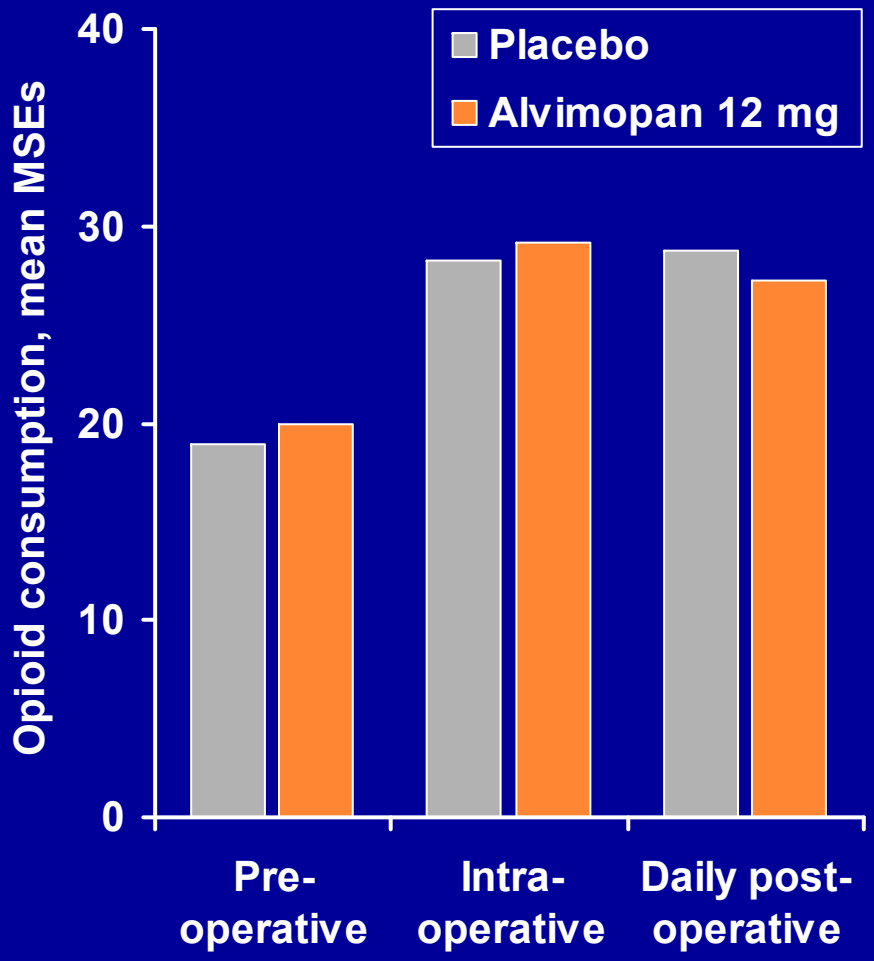


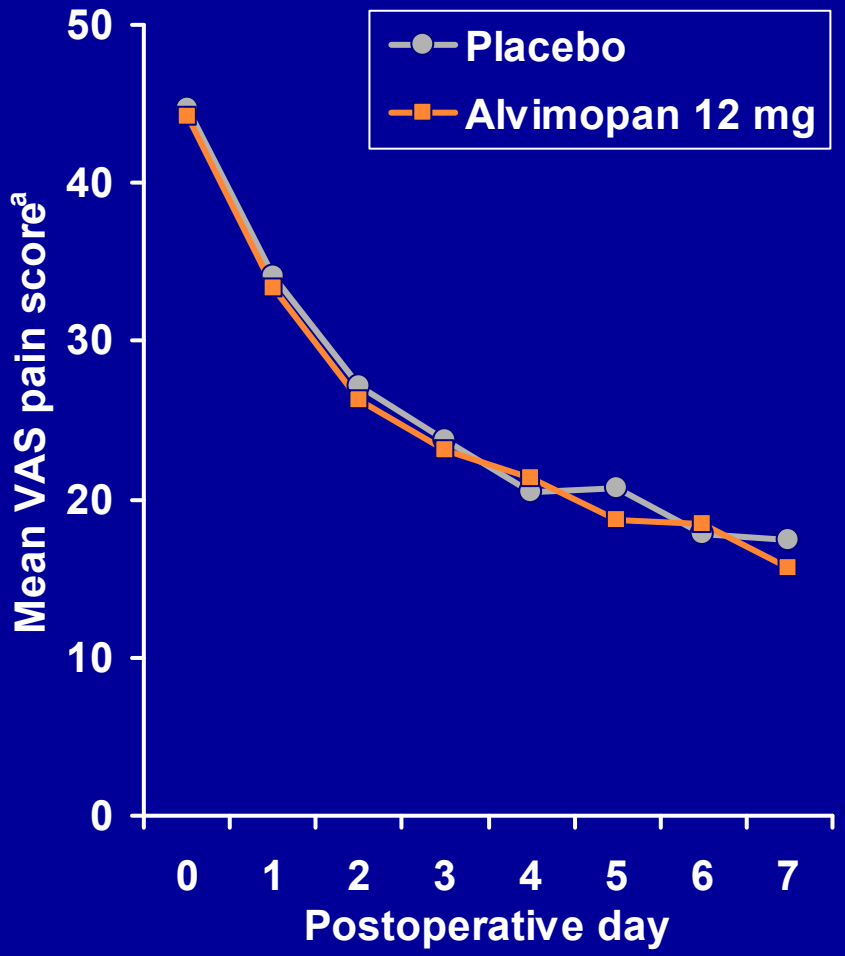
Postoperative NG Tube Insertion
Pooled Studies 314, 313, 308, 302—BR Only



[a] Based on Fisher's exact test.

Postoperative Opioid Consumption
Pooled Studies 314, 313, 308, 302—BR Only





[a] Does not include Study 314.

Presentation Outline

- Mechanism of action
- Phase III clinical trials
- Phase III efficacy results
- Summary

Summary—Efficacy of Alvimopan 12 mg for Management of POI in BR Patients

- Accelerated GI recovery and reduced DOW by ~ 1 day (18 to 26 hr) in studies where ≥ 90% of population BR
  - Higher proportion of GI-2 recovery and DOW responders with NNTs below 10
- Reduction in the incidence of postoperative NG tube insertion by 43%
- No impact on pain management
- Results demonstrate clinically meaningful benefit in BR patients